GENFIT
TOWARDS BETTER MEDICINE

October is National Liver Awareness Month: are you at risk?

AMERICAN LIVER FOUNDATION

GENFIT Pipeline Day
Corporate Presentation

October 19, 2022 | Westin New-York, USA

Disclaimer

This presentation contains certain forward-looking statements, including those within the meaning of the Private Securities Litigation Reform Act of 1995 with respect to GENFIT, including, but not limited to statements about GENFIT's corporate strategy and objectives, the potential sizes of the markets for PBC, cholangiocarcinoma, ACLF, hepatic encephalopathy (HE) and urea cycle disorder (UCD), commercial certainty within these markets and the outcome of the ELATIVE™ phase 3 trial of elafibranor in PBC, development plans our pipeline programs and expected regulatory approvals,. The use of certain words, including "believe, "potential," "expect" and "will" and similar expressions, is intended to identify forward-looking statements. Although the Company believes its expectations are based on the current expectations and reasonable assumptions of the Company's management, these forward-looking statements are subject to numerous known and unknown risks and uncertainties, which could cause actual results to differ materially from those expressed in, or implied or projected by, the forward-looking statements. These risks and uncertainties include, among other things, the uncertainties inherent in research and development, including related to safety, progression of, and results from, its ongoing and planned clinical trials, review and approvals by regulatory authorities of its drug and diagnostic candidates, the impact of the COVID-19 pandemic, the effects of the competitive landscape, inflation and fluctuations in exchange rates and market and general economic conditions, and the Company's continued ability to raise capital to fund its development, as well as those risks and uncertainties discussed or identified in the Company's public filings with the French Autorité des marches financiers ("AMF"), including those listed in Section 2 "Risks Factors and Internal Control " of the Company's 2021 Registration Document ("Document d'Enregistrement Universel") filed with the AMF on April 29, 2022, which is available on GENFIT's website (www.genfit.com) and on the website of the AMF(www.amf-france.org) and public filings and reports filed with the U.S. Securities and Exchange Commission ("SEC"), including the Company's Form 20-F
document filed with the SEC on the same date, and subsequent filings and reports filed with the AMF or SEC, including the Half-Year Business and Financial Report at June 30, 2022 or otherwise made public, by the Company.
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Introduction

Objective of this PIPELINE Day

Pascal Prigent, CEO of GENFIT

Agenda

- *Primary Biliary Cholangitis (PBC)*
- **Acute on-chronic liver failure (ACLF)**
- **Hepatic encephalopathy (HE)**
- **Cholangiocarcinoma (CCA)**
- **Urea cycle disorder (UCD) & and organic acidemia disorder (OAD)**

Closing remarks

GENFIT
TOWARDS BETTER MEDICINE

Acute on-chronic liver failure (ACLF)

Disease state

- *Jennifer C. Lai, MD, MBA, Transplant hepatologist, University of California, San Francisco (UCSF), USA – Endowed Professorship of Liver Health & Transplantation*

Acute-on-Chronic Liver Failure (ACLF)

Jennifer C. Lai, MD, MBA
Transplant Hepatologist
Endowed Professor of Liver Health & Transplantation
University of California, San Francisco (UCSF)

Financial Disclosures

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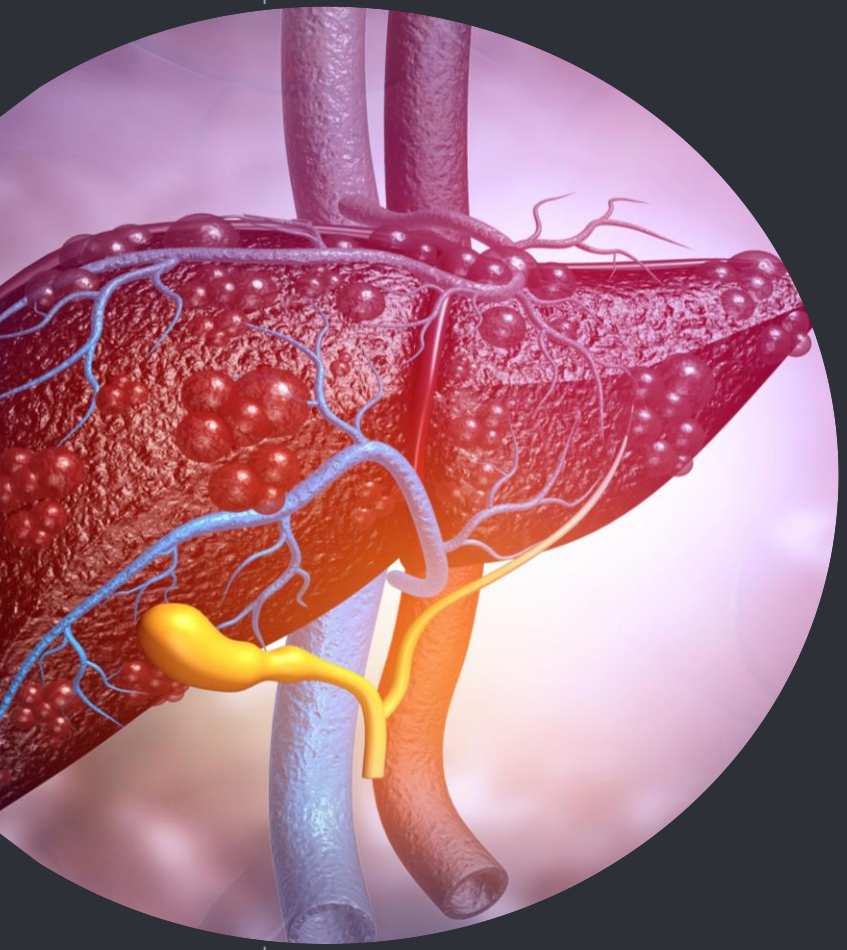
- Axcella Health, Inc
- Gore Medical
- Grifols

Other paid commitments:

- Novo Nordisk (Advisory Board)
- U.S. FDA Gastrointestinal Drug Advisory Committee (Member)
- Associate Editor (*Hepatology* journal)

Acute-on-Chronic Liver Failure : Defined



…a potentially reversible condition in patients with chronic liver disease with or without cirrhosis that is associated with potential for multiple organ failure and high mortality within 3 months in the absence of treatment…

Bajaj J, *et al*. Am J Gastro 2022.

“ There is no direct therapeutic for ACLF.

SCOPE OF THE UNDERLYING PROBLEM :

Chronic liver disease & cirrhosis

Chronic Liver Disease & Cirrhosis

11th most common cause of death

2 million deaths worldwide (~4% of deaths worldwide)

2 billion consume alcohol

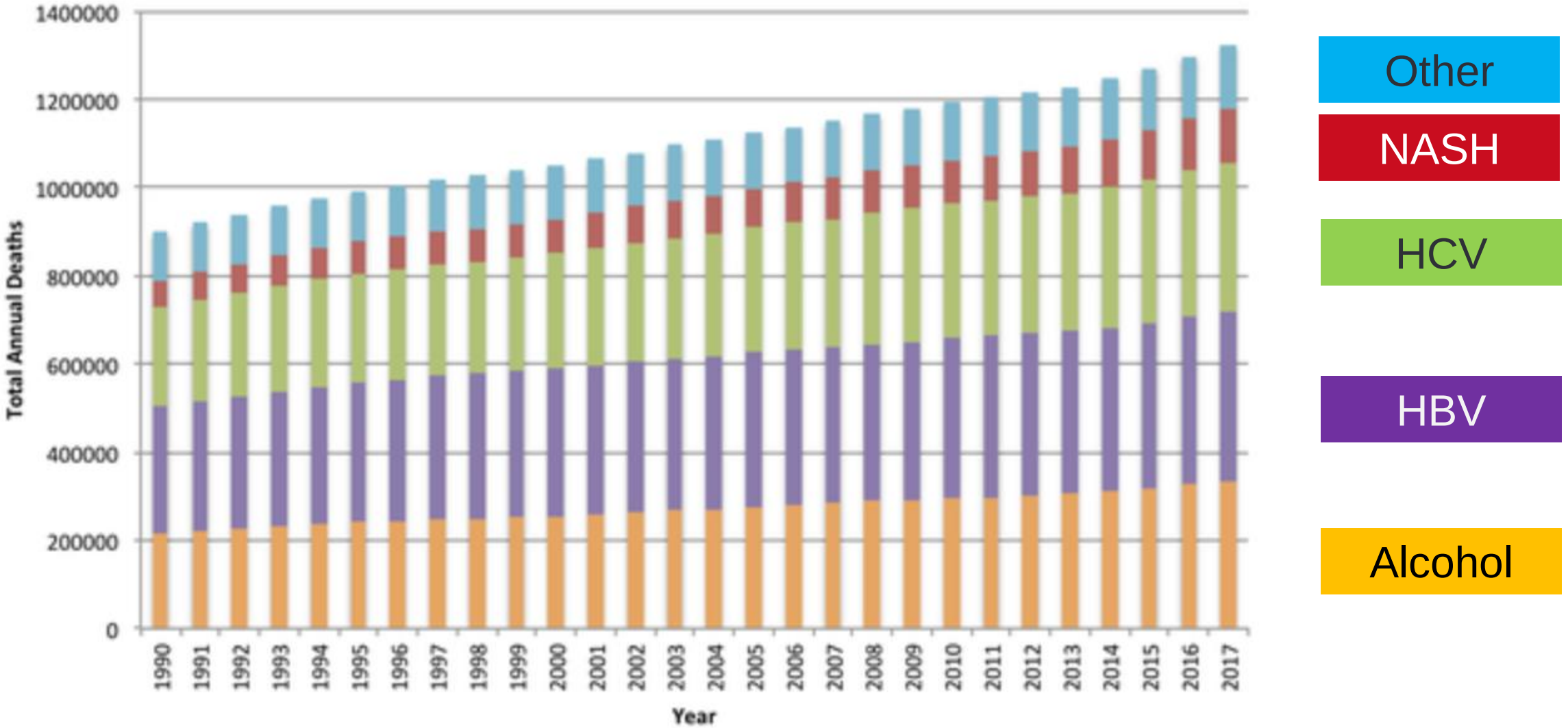
At risk for alcohol-associated liver disease / cirrhosis

2 billion overweight/obese

At risk for non-alcoholic fatty liver disease / cirrhosis

Asrani S, *et al*. J Hep 2019.

Deaths by liver disease etiology : RISING



Cheemerla S, *et al*. Clin Liv Dis 2021. https://vizhub.healthdata.org/gbd-results/

Economic burden of chronic conditions in the U.S. : Cirrhosis and ACLF much higher!

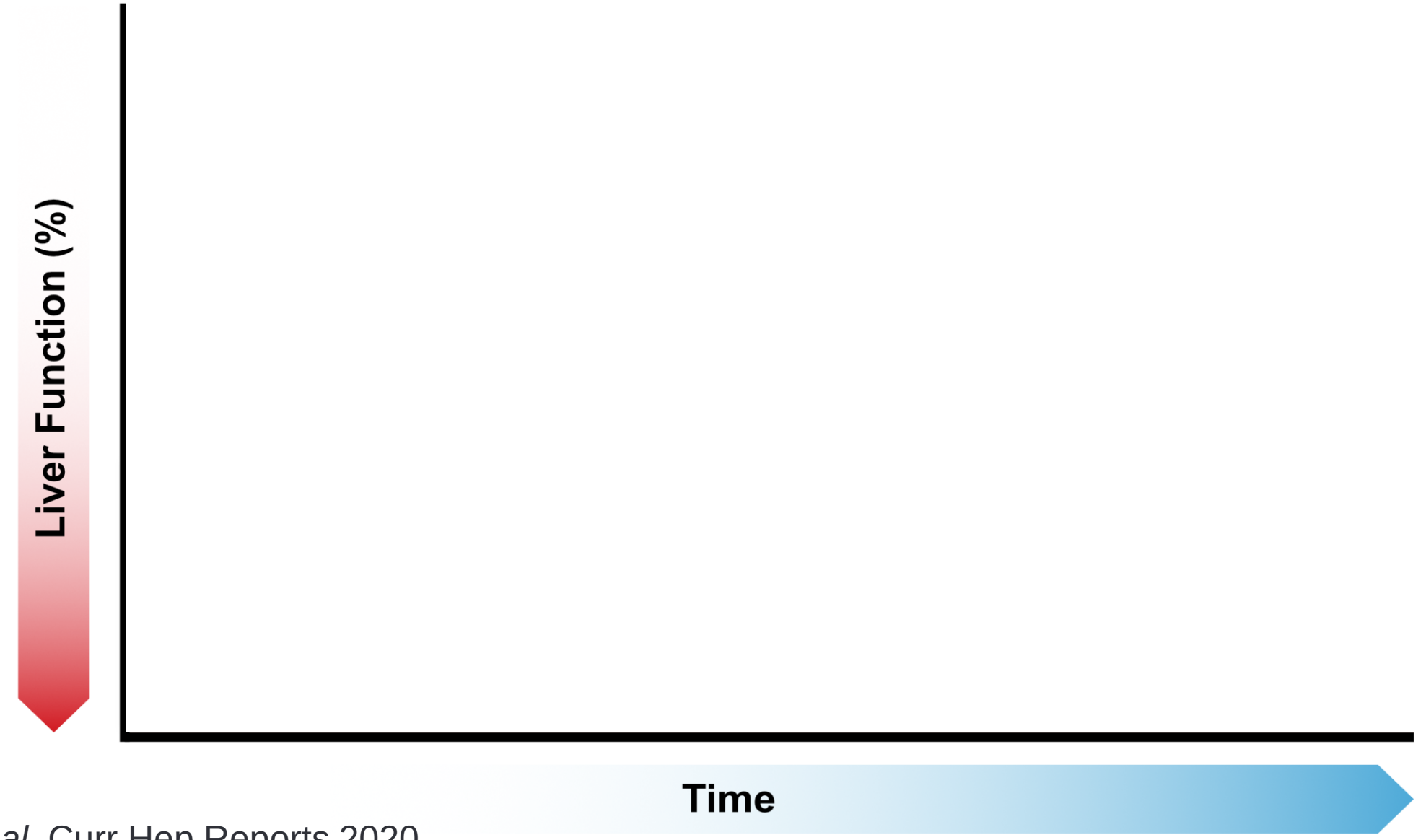
Chronic disease	Length of hospital stay	Inpatient mortality	Mean cost per hospitalization
Pneumonia	5 days	3.3%	$7,581
Congestive heart failure	5 days	3.0%	$8,315
Cerebrovascular disease	6 days	4.7%	$8,117

Allen A, *et al*. Hepatol 2016.

THE PATIENT :

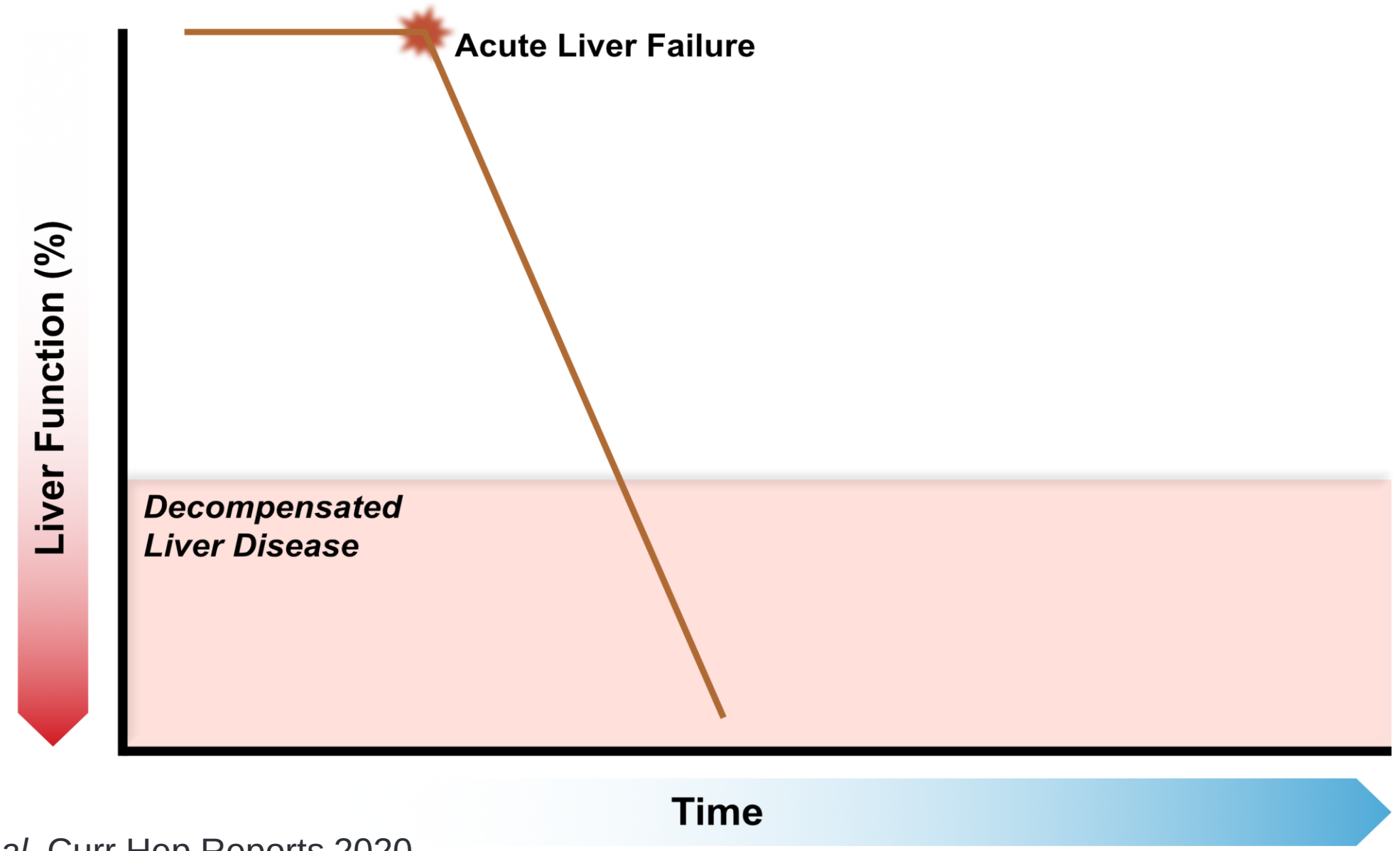
Clinical Course & Features

Trajectories of liver function in 3 common liver states



Mahmud N, *et al*. Curr Hep Reports 2020.

Trajectories of liver function in 3 common liver states



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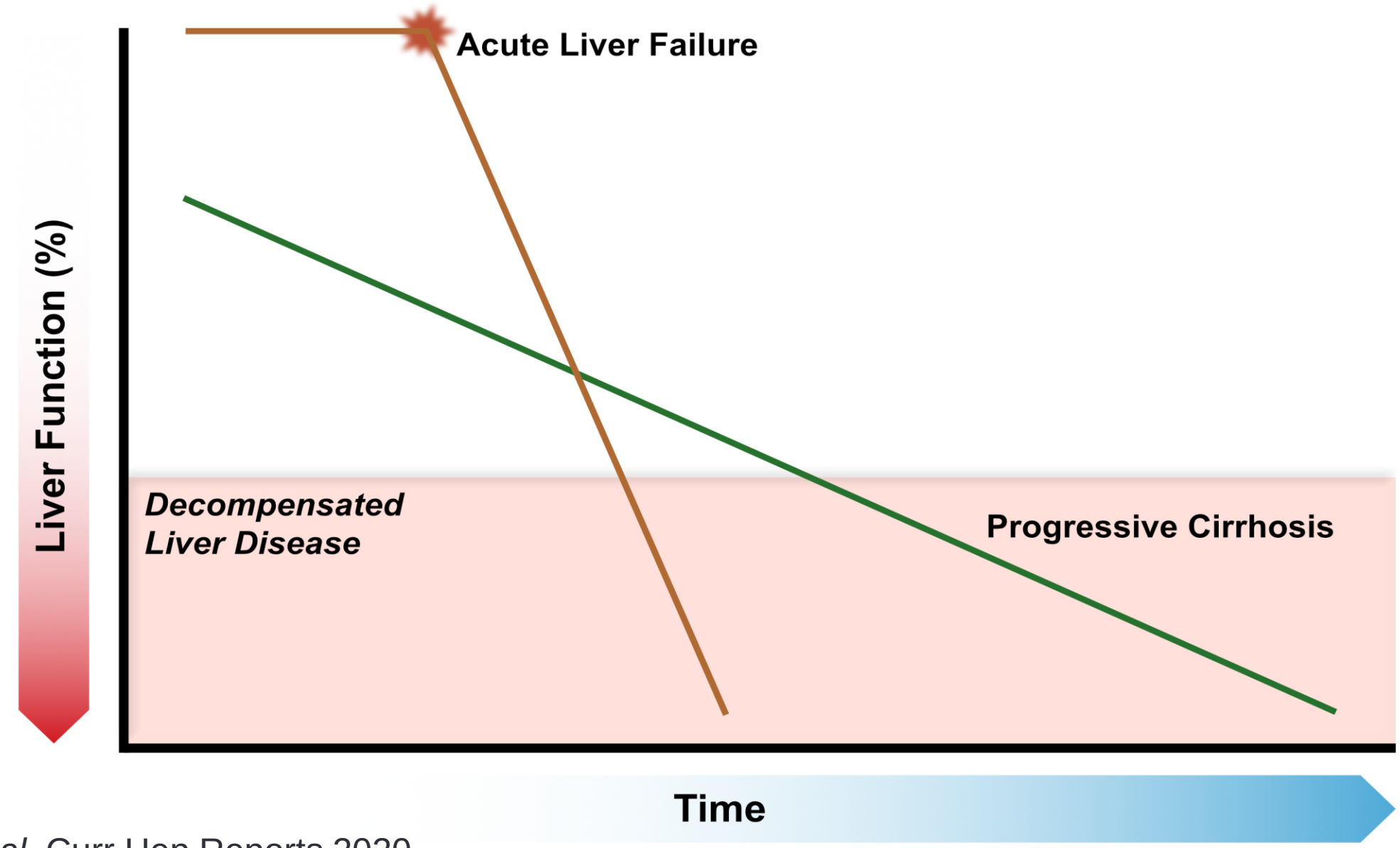

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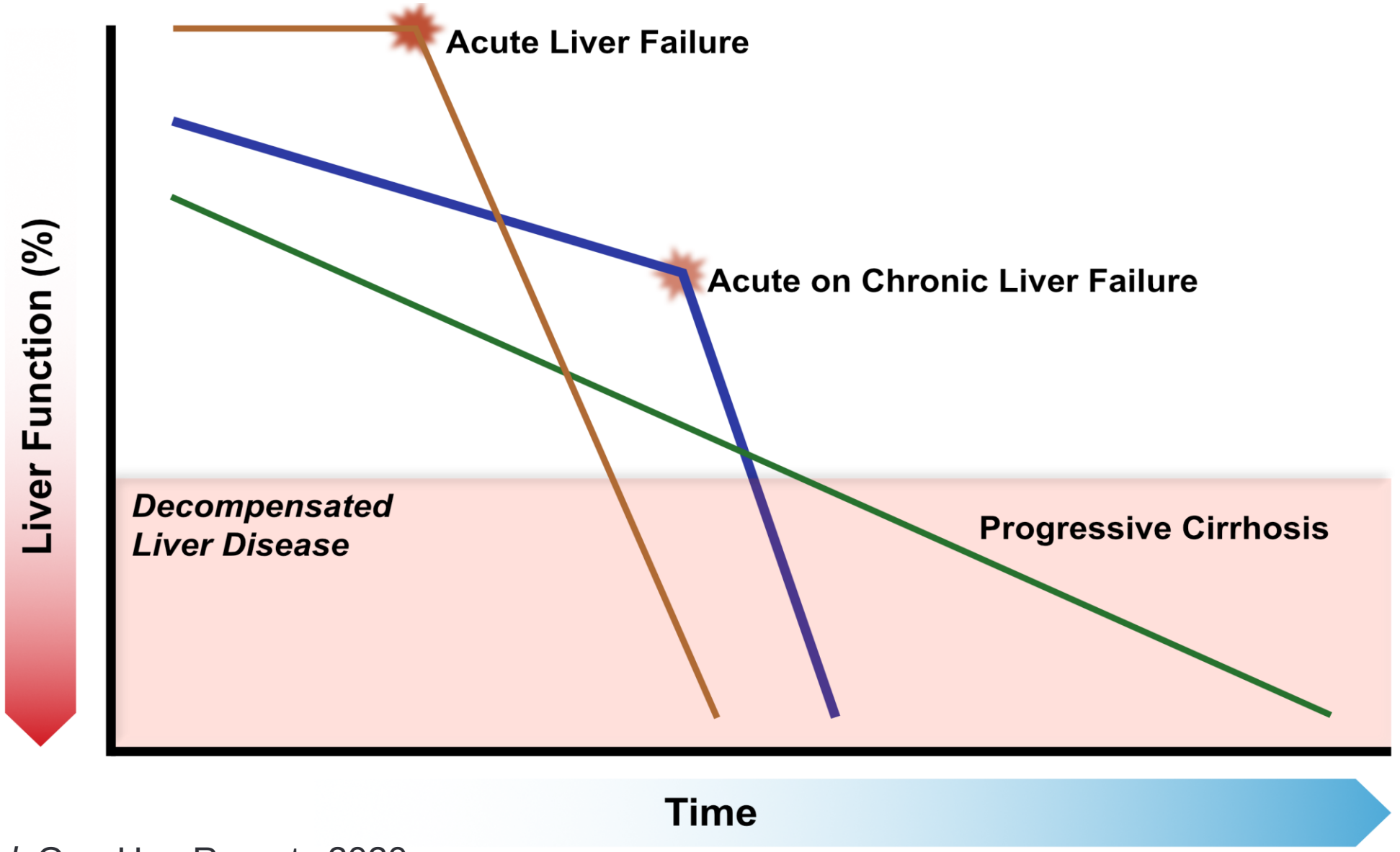


Mahmud N, *et al*. Curr Hep Reports 2020.

Clinical characteristics (U.S. cohort)

	n=1,031
Age (years)	57 (11)
Men	66%
Liver disease etiology	
Alcohol only	31%
HCV only	21%
Alcohol + HCV	15%
NASH	17%
Other	15%

Reason for admission	n=1,031
Bacterial infection	25%
GI bleed	16%
Hepatic enceph.	17%
Renal dysfxn	12%
Alcohol related	4%
Electrolytes abnl	3%
Other	23%

Wong F, *et al*. Liver Transpl 2022.

Role of prior hepatic decompensation

	n=417
No prior event	26%
<3 months prior	16%
3-12 prior	17%
>12 months prior	41%

Moreau R, *et al*. Gastroenterol 2013.

Percent with *extra-hepatic* organ failure on admission

RENAL

50%

NEUROLOGIC

22%

CIRCULATORY

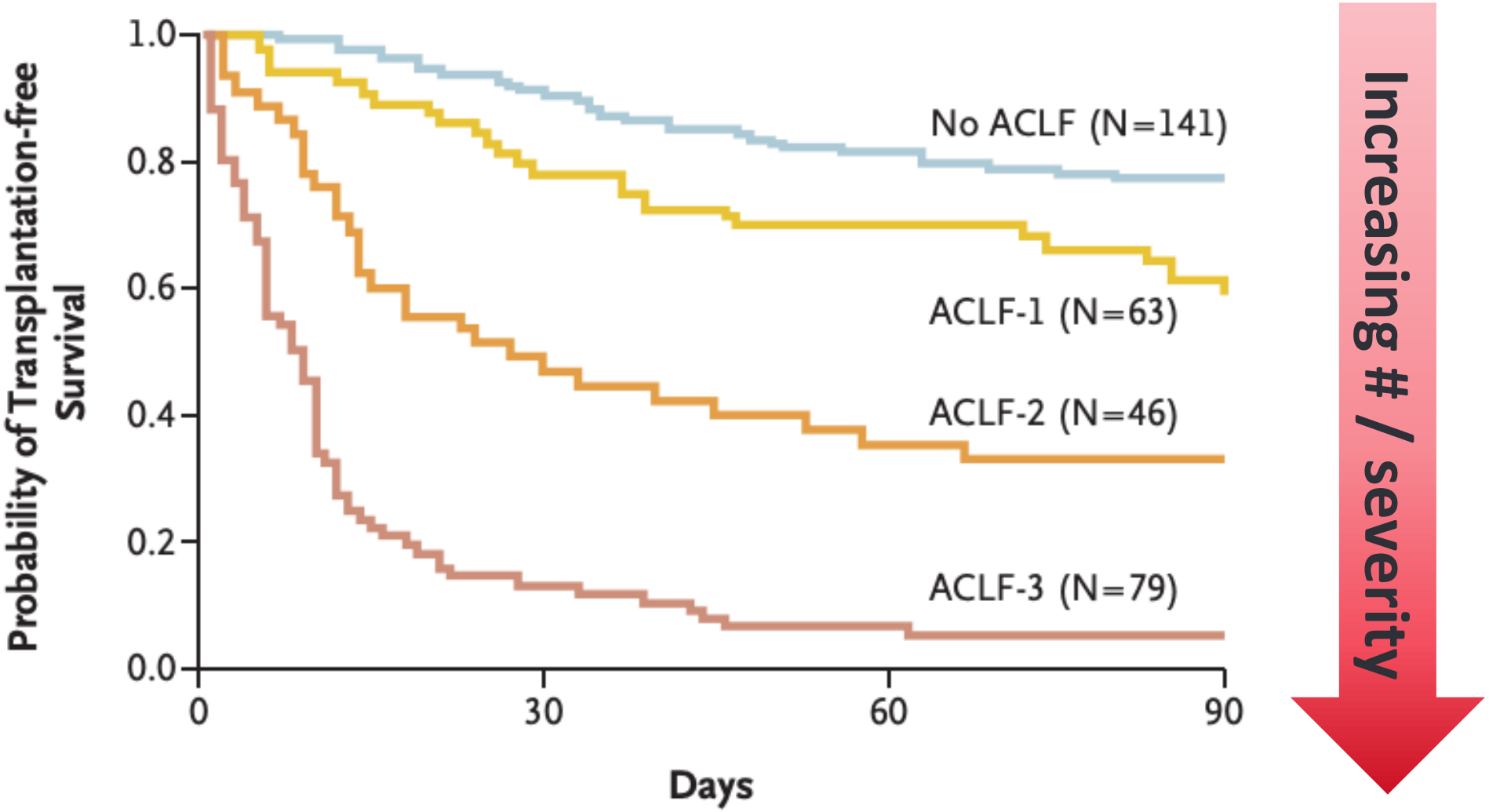
23%

RESPIRATORY

13%

Arroyo V, *et al*. J Hepatol 2015.

Probability of survival by ACLF severity



The greater the number/severity of organ failures, the greater the risk of death.

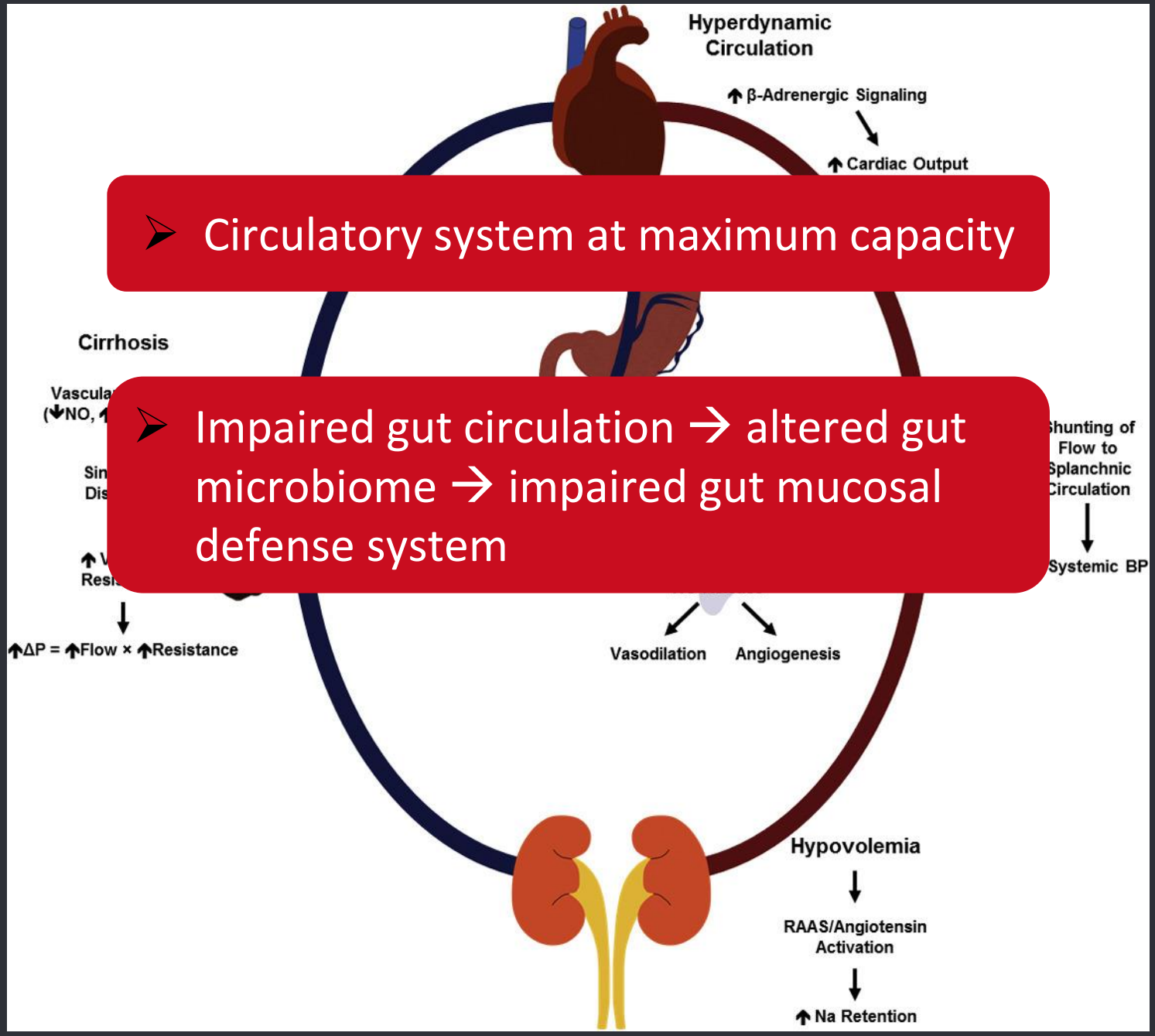
Gustot T, *et al*. Hepatol 2015. Arroyo V, *et al*. NEJM 2020.

PATHOGENESIS :

Leading hypotheses and supporting data

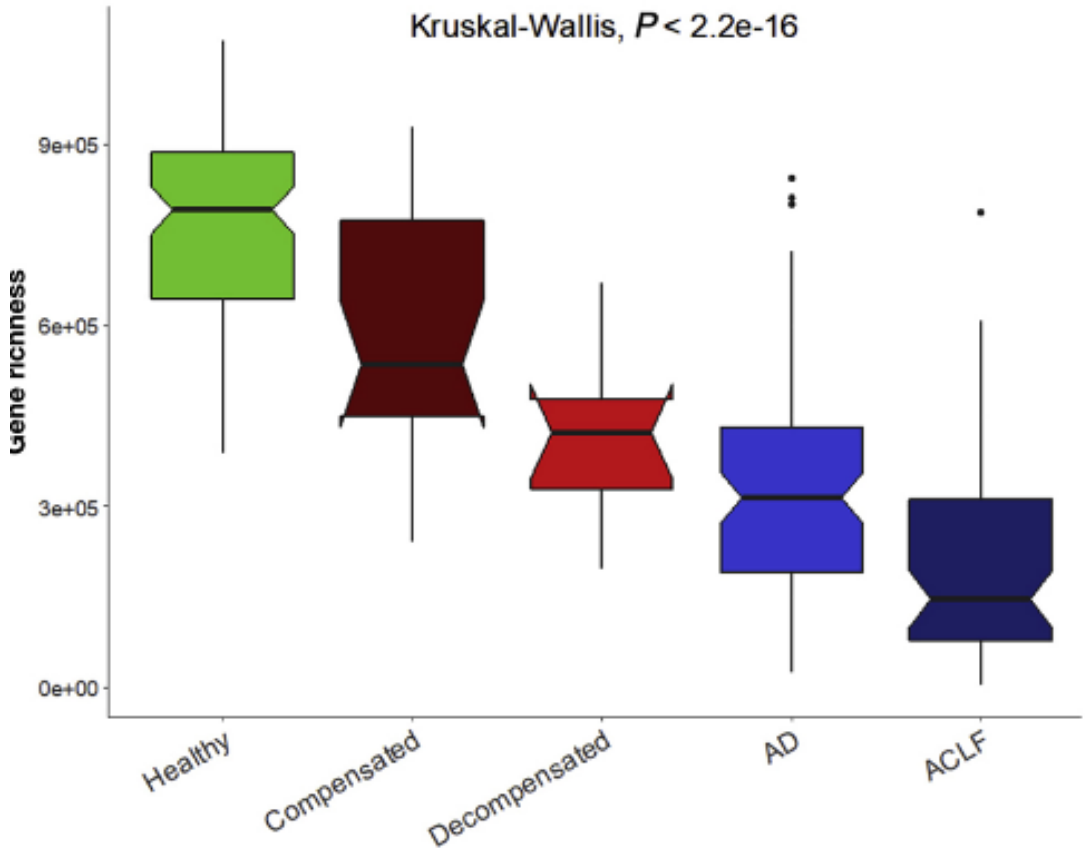
The underlying condition

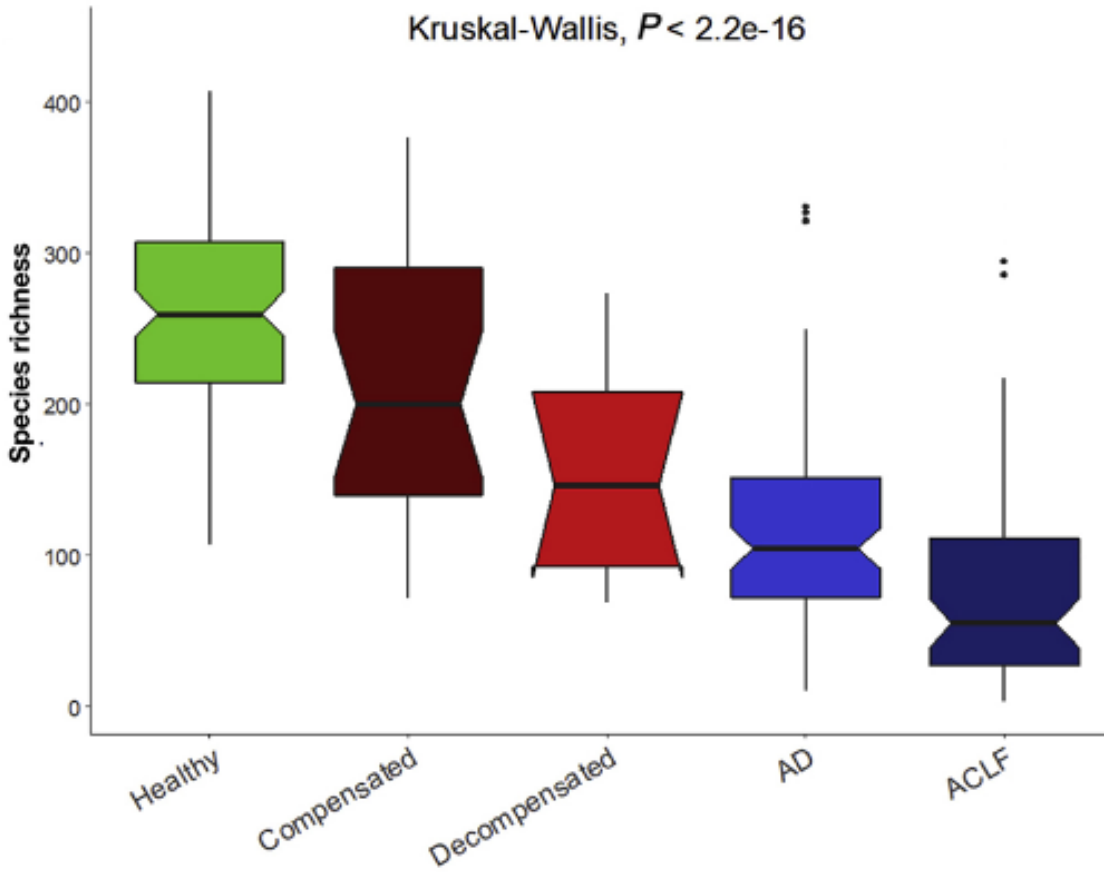
Portal hypertension 101



Simonetto DA, *et al*. Mayo Clinic Proc 2019.

Greater severity of liver disease is associated with less diverse microbiome

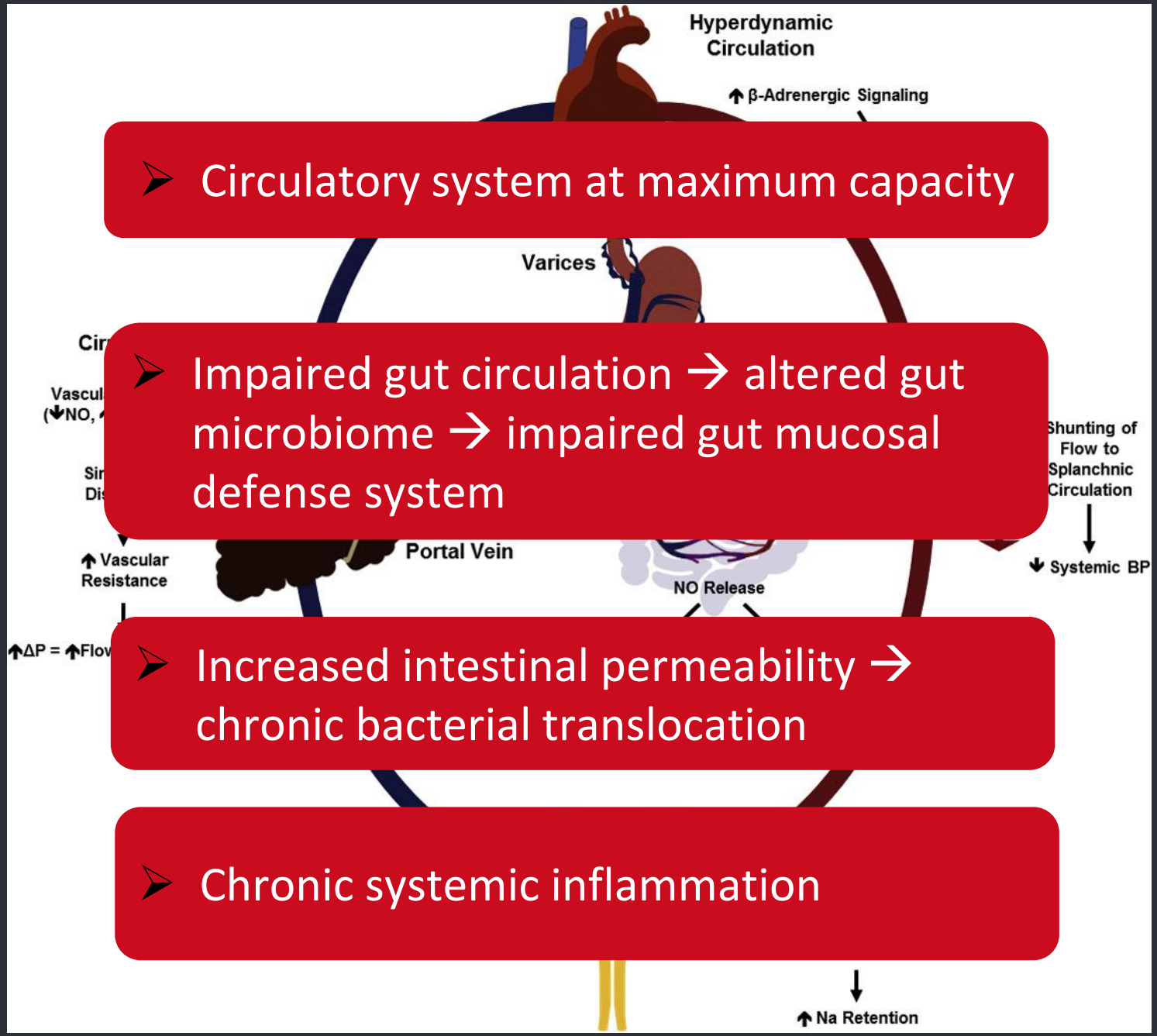




Sole C, *et al*. Gastroenterol 2021.

The underlying condition

Portal hypertension 101

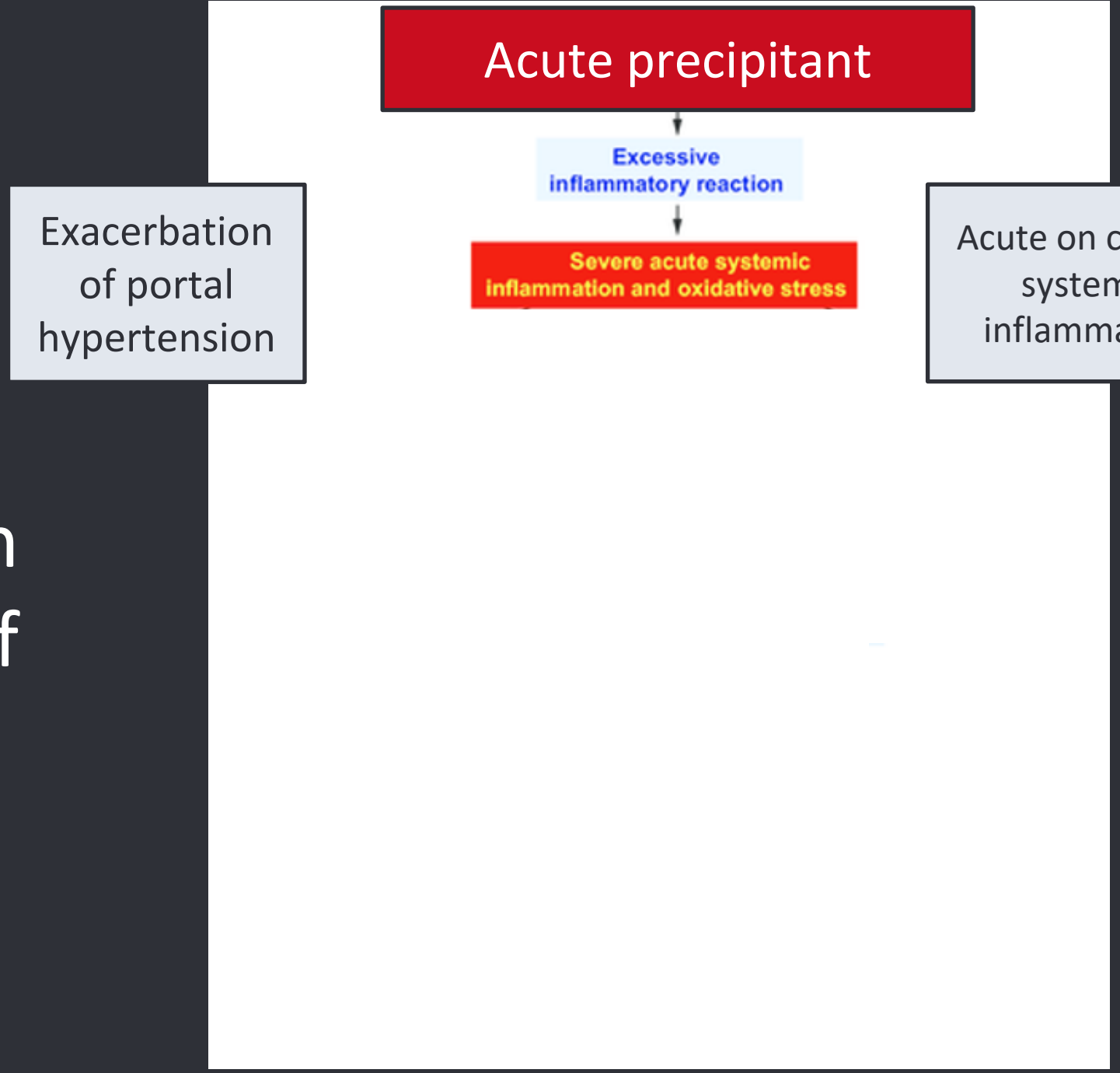


- Circulatory system at maximum capacity
- Impaired gut circulation → altered gut microbiome → impaired gut mucosal defense system
- Increased intestinal permeability → chronic bacterial translocation
- Chronic systemic inflammation

Simonetto DA, *et al*. Mayo Clinic Proc 2019.

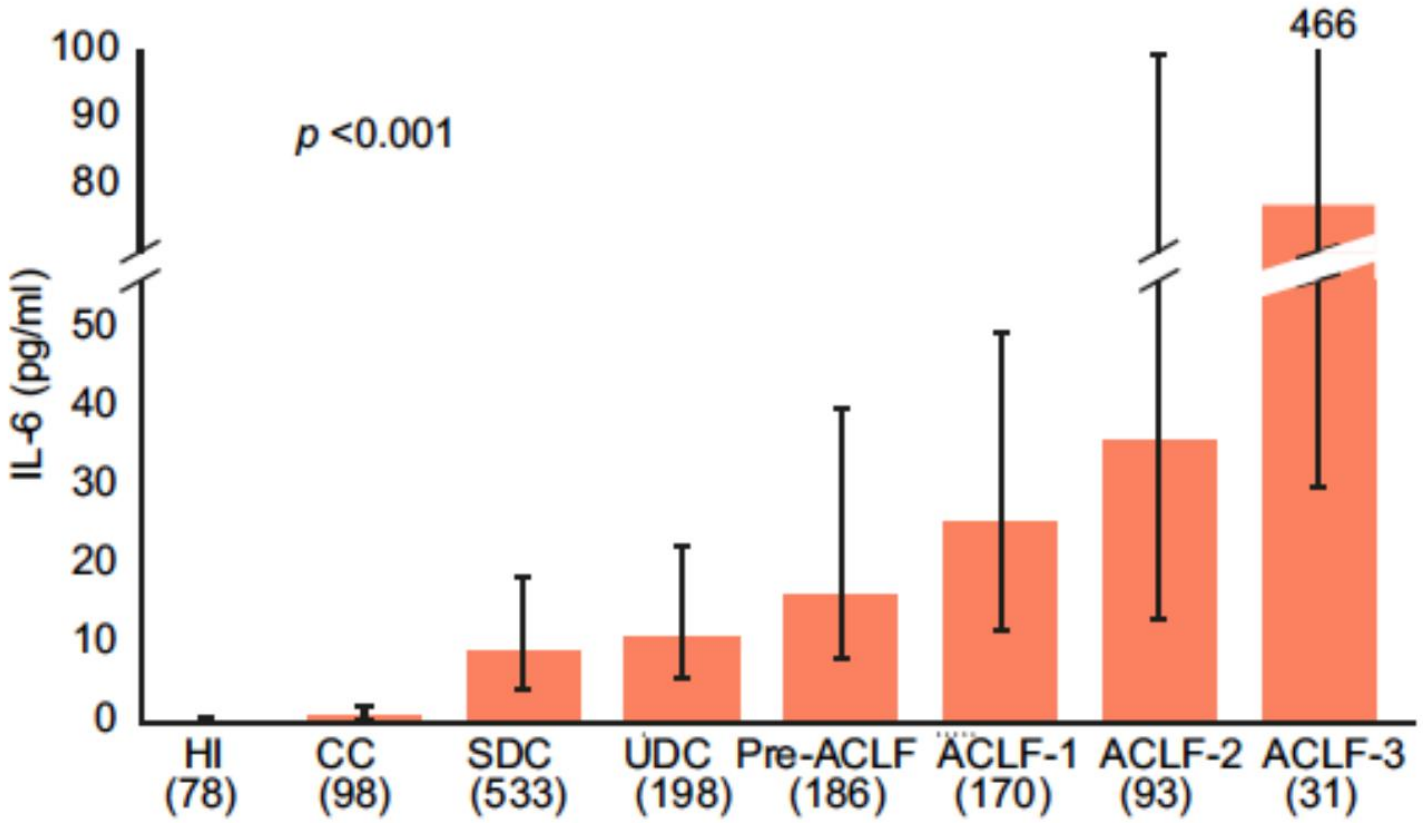
The acute insult

- Systemic inflammation hypothesis of ACLF



Arroyo V, *et al*. J Hep 2021.
Fig adapted from Arroyo V, *et al*. J Hepatol 2014.

Systemic inflammatory markers are elevated



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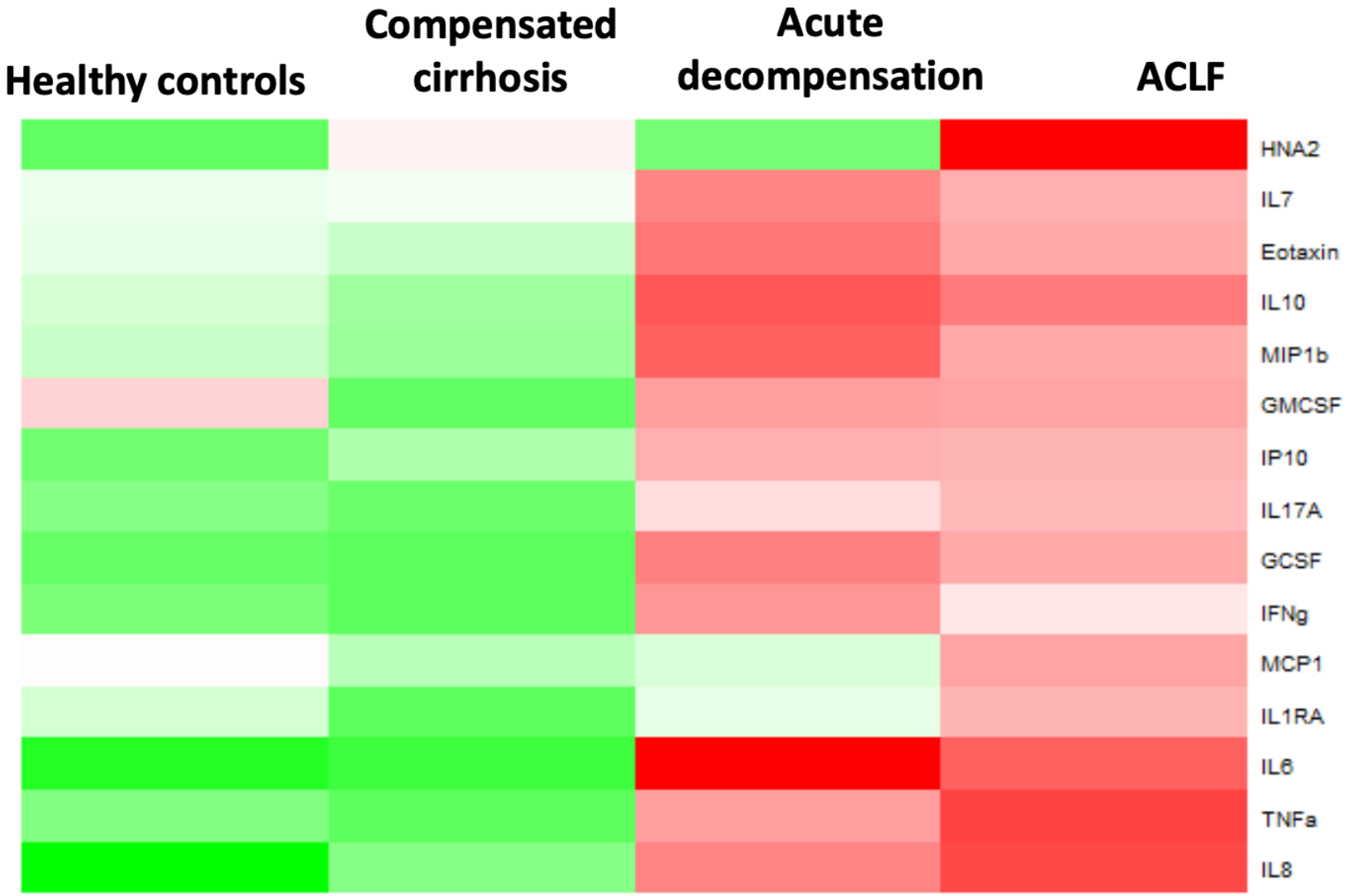
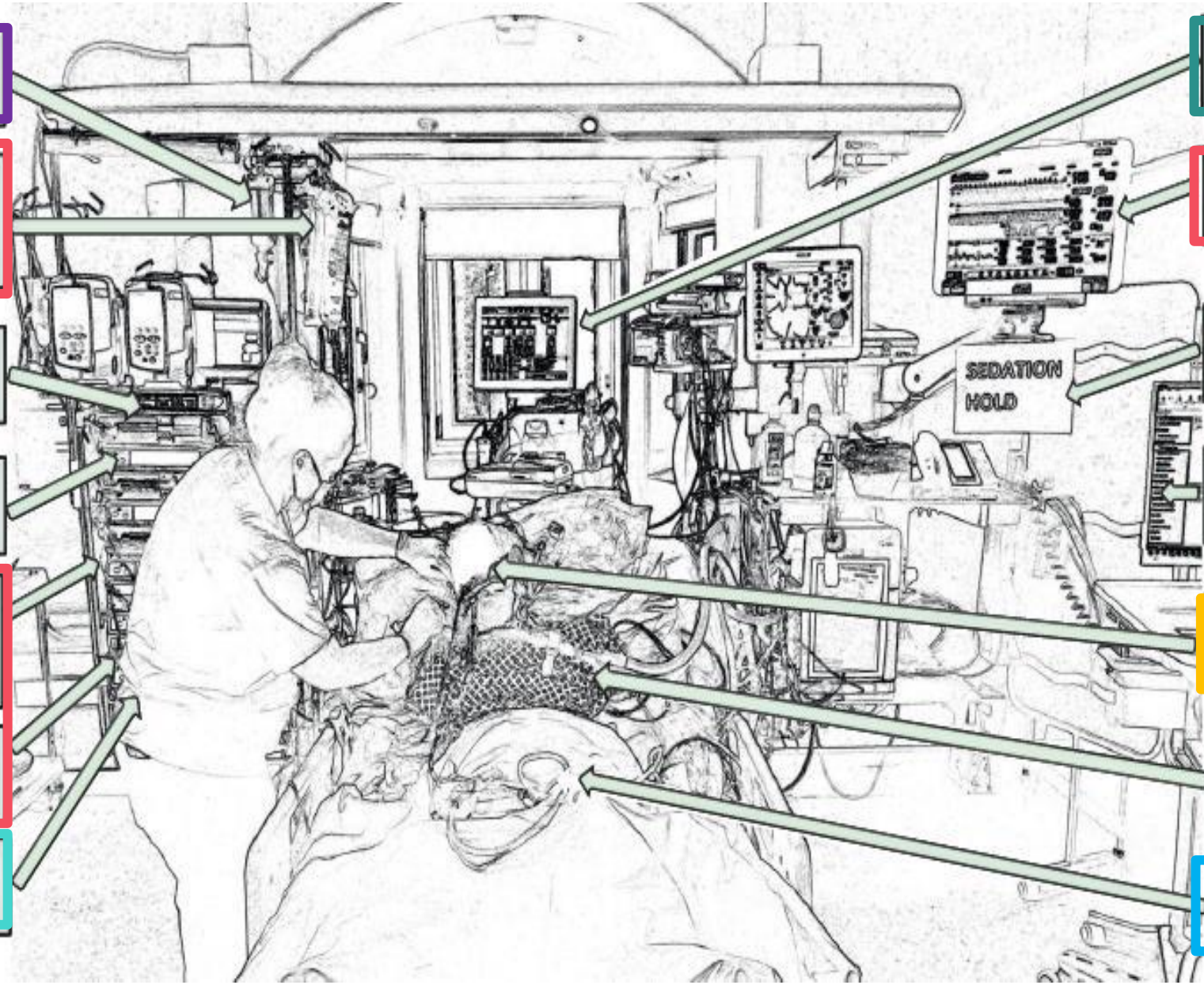


Trebicka J, *et al*. Front Immunol 2019.

AT THE BEDSIDE :

Management

“ There is no direct therapeutic for ACLF.



Enteral nutrition via nasogastric tube

Monitored circulating volume expansion with intravenous fluids

Insulin infusion for glycaemic stability

Electrolyte infusion for metabolic stability

Noradrenalin/ terlipressin for cardiovascular support

Hydrocortisone for adrenal insufficiency

Nursing staff experienced in liver care

Continuous haemofiltration for acute kidney injury

Haemodynamic monitoring for cardiovascular stability

Encephalopathy: minimal use of sedation

Serial illness severity assessment

Encephalopathy: intubation for airway protection

Ascitic decompression for tense ascites

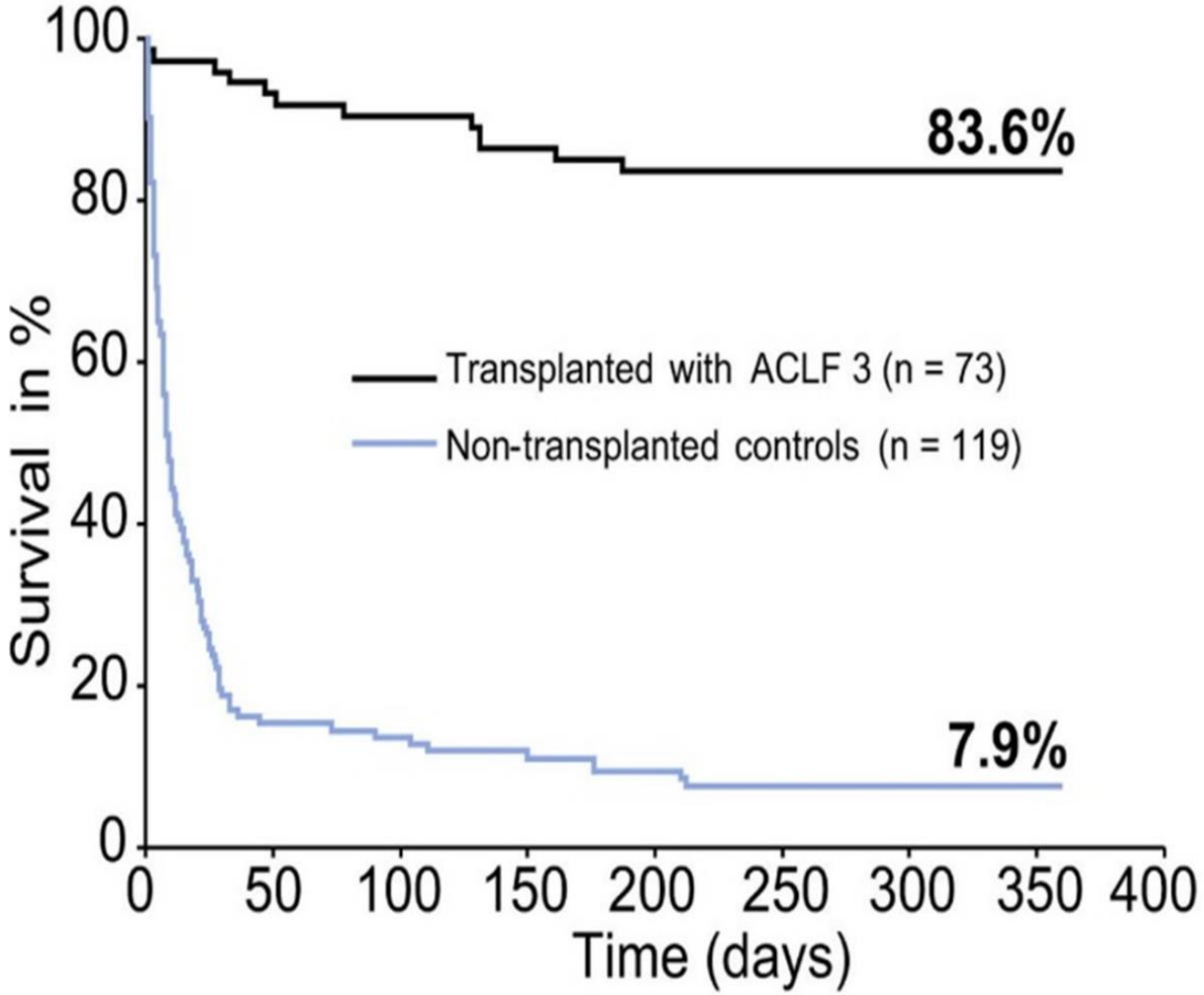
Microbial cultures to guide antibiotic selection

Bernal W, *et al*. J Hepatol 2021.

GOAL OF TREATMENT : BUY TIME

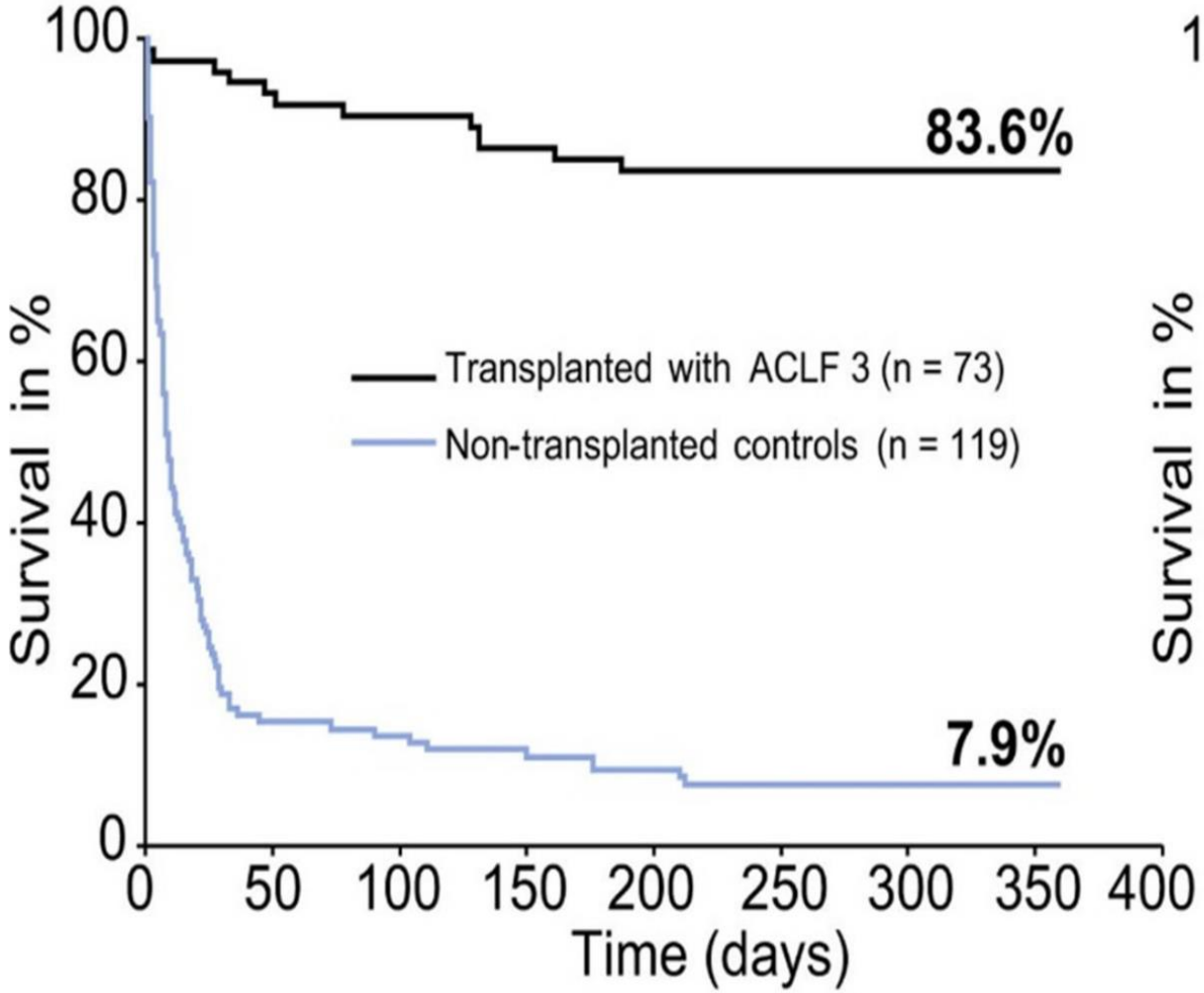
- Allow the precipitant to resolve
- To allow families to say goodbye
- To prepare for liver transplant

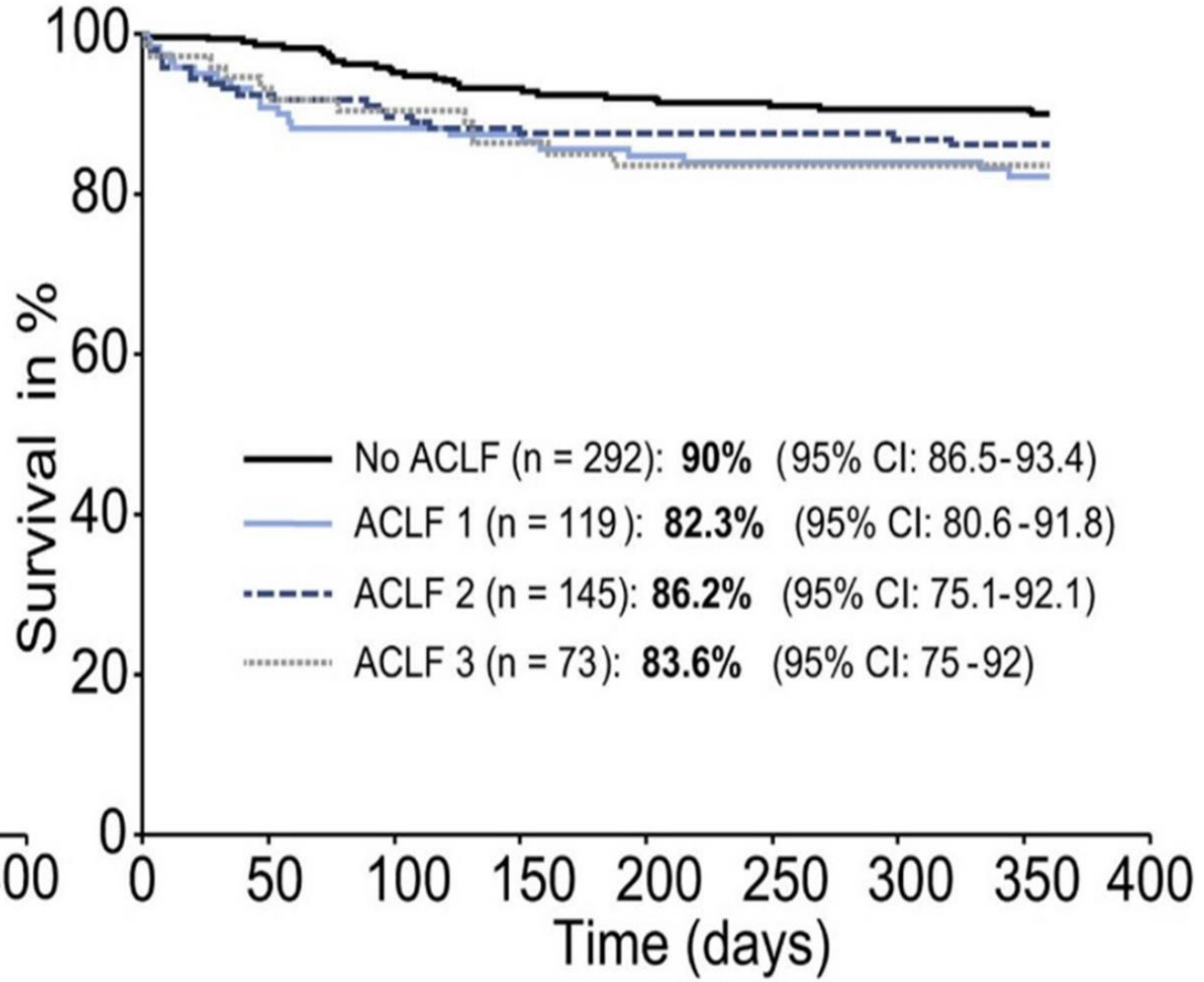
Survival is better with transplant than without



Gustot, *et* al. Hepatol 2015. Artru F, *et al*. J Hep 2017.

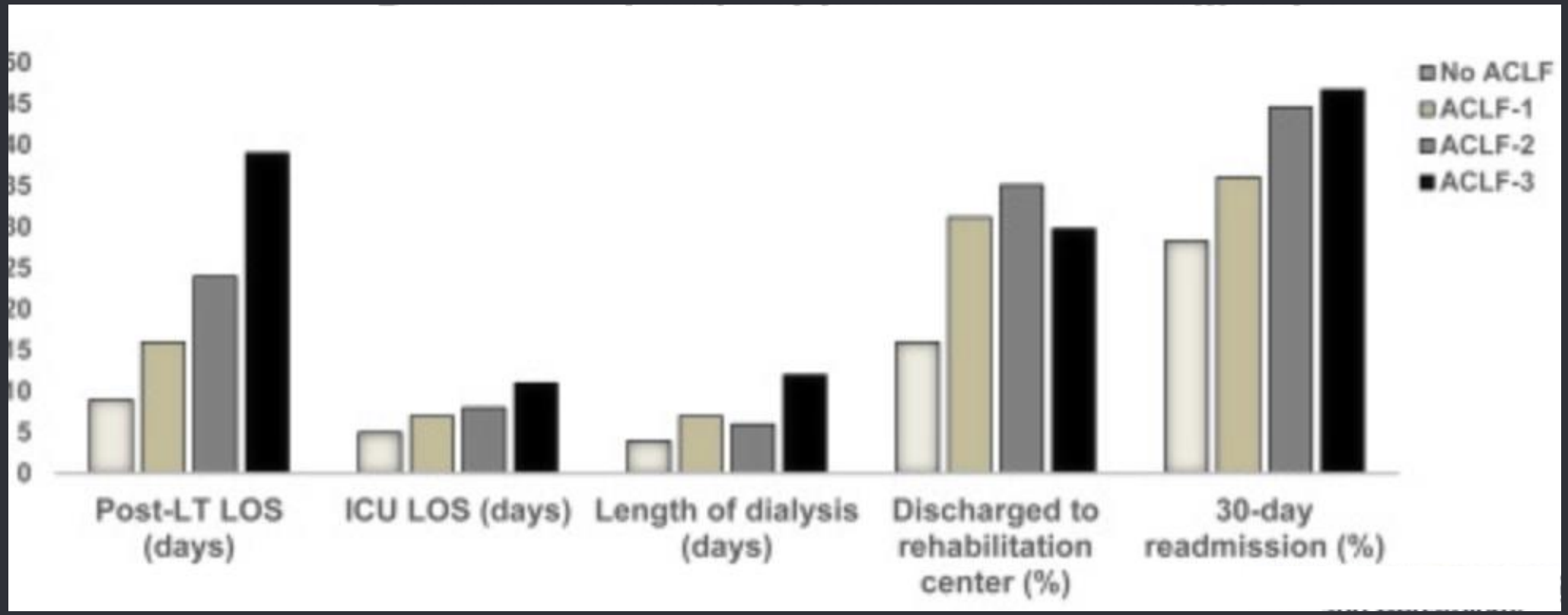
Transplant survival is acceptable in all ACLF grades





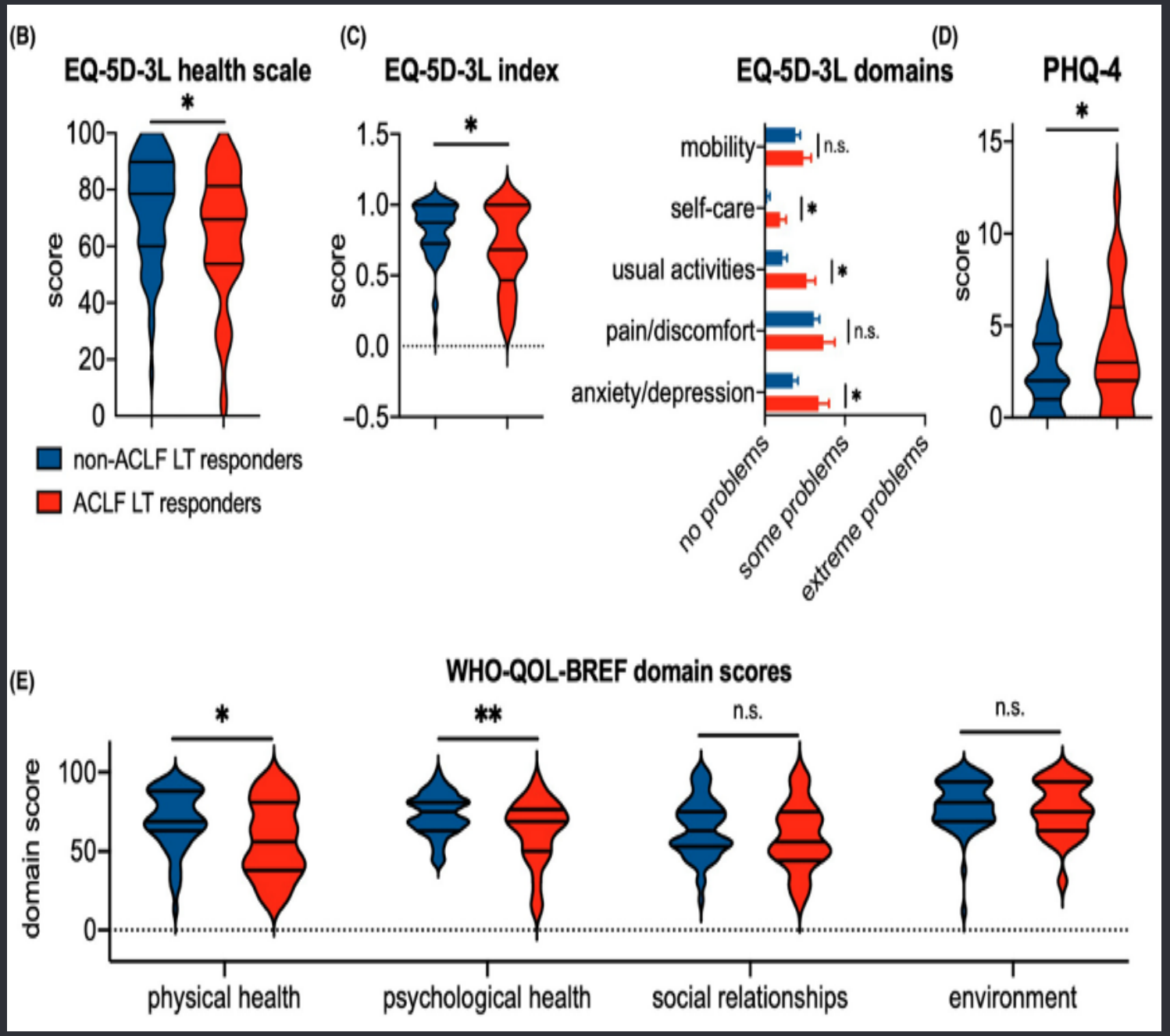
Gustot, *et* al. Hepatol 2015. Artru F, *et al*. J Hep 2017.

Post-transplant healthcare utilization increases by stage of ACLF



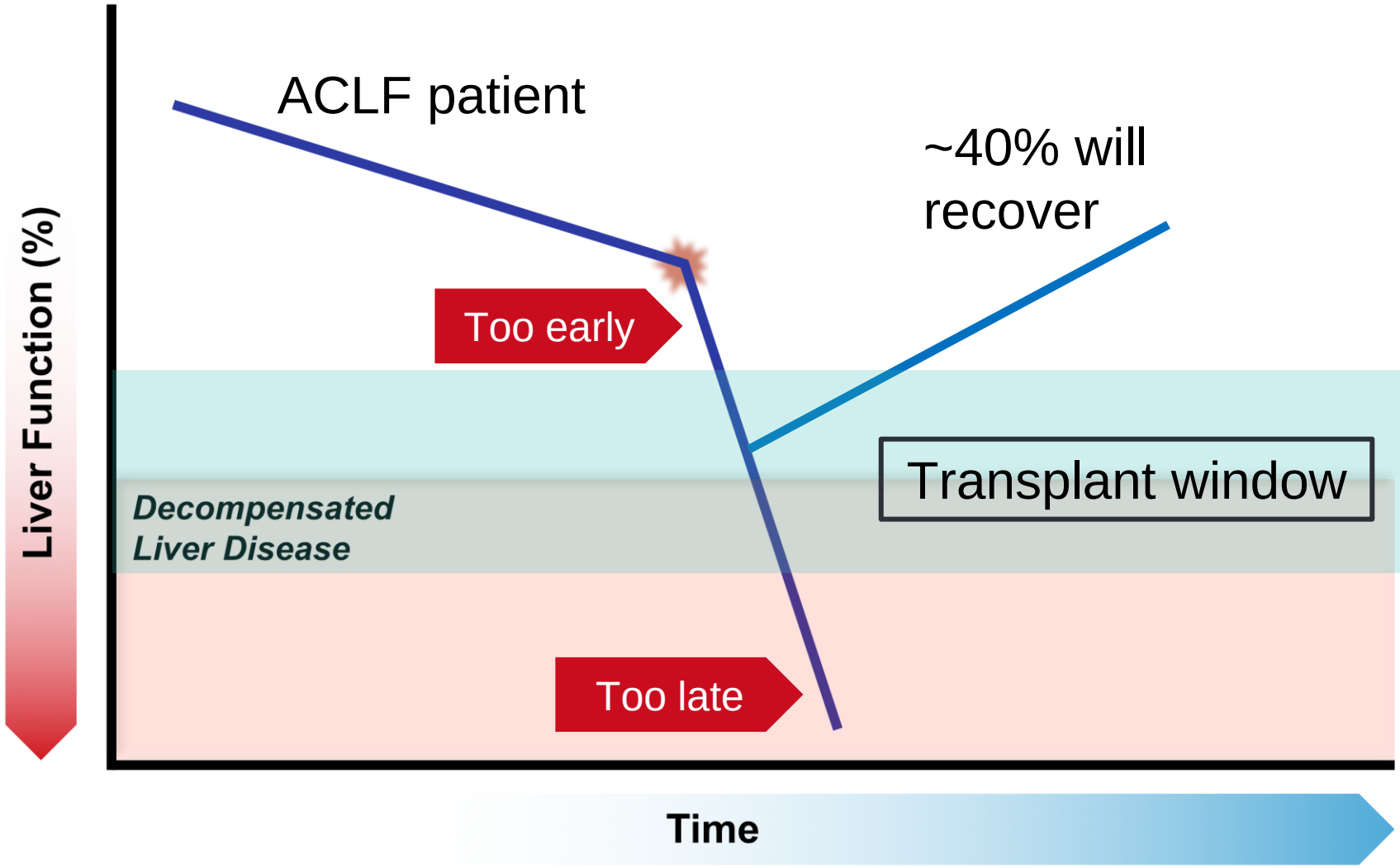
Sundaram V, *et al*. Clin Gastro Hep 2022.

Post-LT quality of life is significantly impaired



Sundaram V, *et al*. Clin Gastro Hep 2022.

Narrow window for liver transplantation



- ~4% of patients with cirrhosis are listed for liver transplant
- 1 in 4 patients listed for transplant die while waiting

Adapted from Mahmud N, *et al*. Curr Hep Reports 2020 and Gustot T, *et al*. J Hepatol 2018. Atiemo *et al*. AJT 2017.

Interventions other than liver transplantation :
Statements from the ACG ACLF guidelines

- Artificial liver support systems

  "whether they provide any clinical benefit is unclear"

- Plasma exchange

  "its effect in ACLF is unknown"

- Granulocyte colony stimulating factor

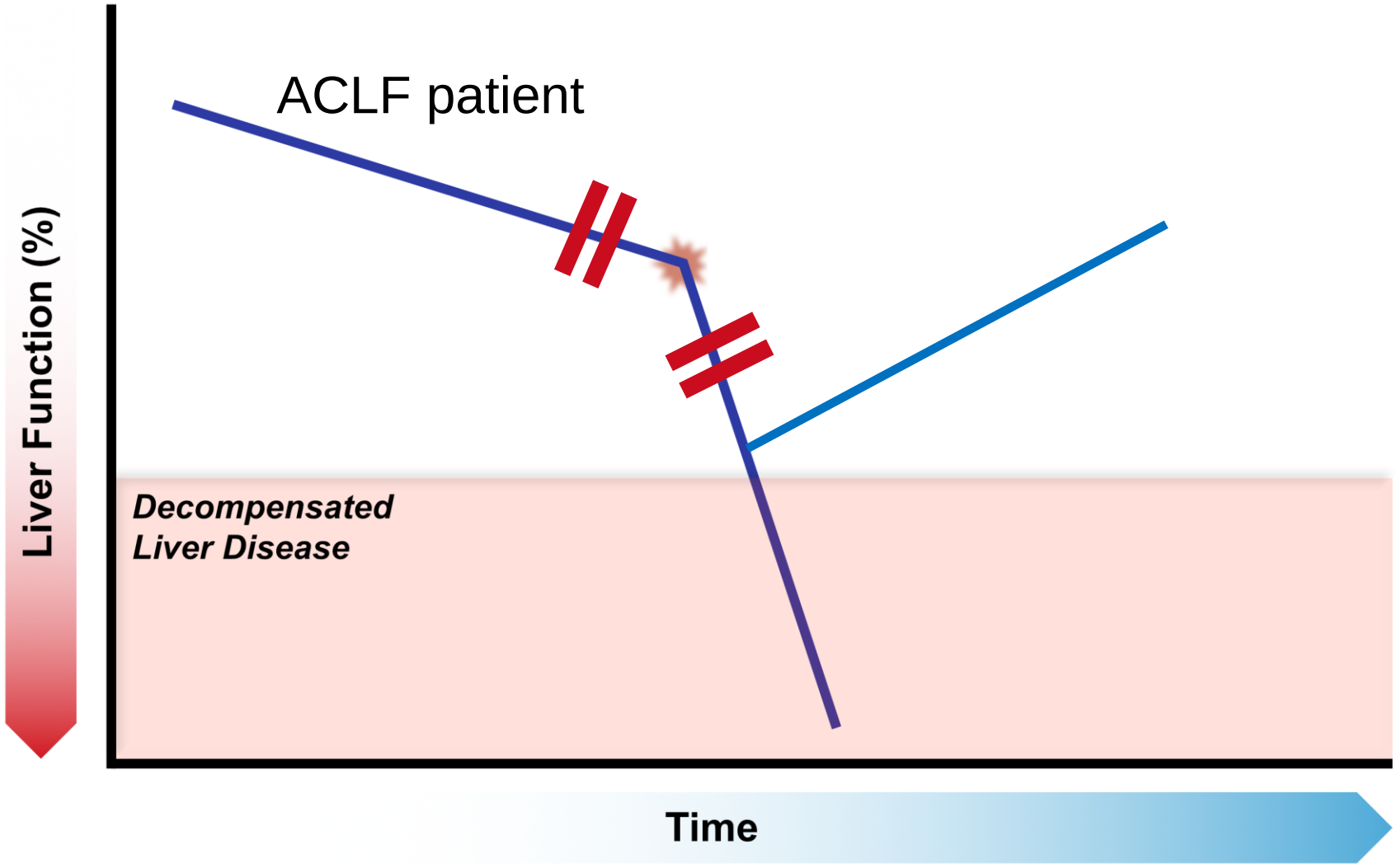
  "we suggest against the use of G-CSF"

- Stem cell therapy

  "evidence to support its use is currently insufficient"

Bajaj J, *et al*. Am J Gastro 2022.

The Opportunity



Adapted from Mahmud N, *et al*. Curr Hep Reports 2020 and Gustot T, *et al*. J Hepatol 2018.

Key Points : ACLF (Disease state)

- ACLF is a highly lethal, resource-intensive condition that occurs in patients with chronic liver disease.
- Portal hypertension, altered microbiome, and systemic inflammation drive ACLF.
- There is no direct therapeutic for ACLF.
  - Liver transplantation, while effective, is limited due to narrow timing, low availability of organs, and poor access to high-level care.

Short Q&A (10 minutes)

Questions?

Acute on-chronic liver failure (ACLF)

GENFIT's programs

VS-01-ACLF*

- *Vincent Forster, PhD, GENFIT, co-founder of VERSANTIS*
- *Prof Katharina Staufer, MD, GENFIT, Chief Medical Officer of VERSANTIS*

NTZ*

- *Dean Hum, PhD, Chief Scientific Officer of GENFIT*
- *Carol Addy, MD, Chief Medical Officer of GENFIT*

* VS-01 and NTZ are investigational drugs that are not approved by any Health Authority for treatment of ACLF.

Acute on-chronic liver failure (ACLF)

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NTZ*

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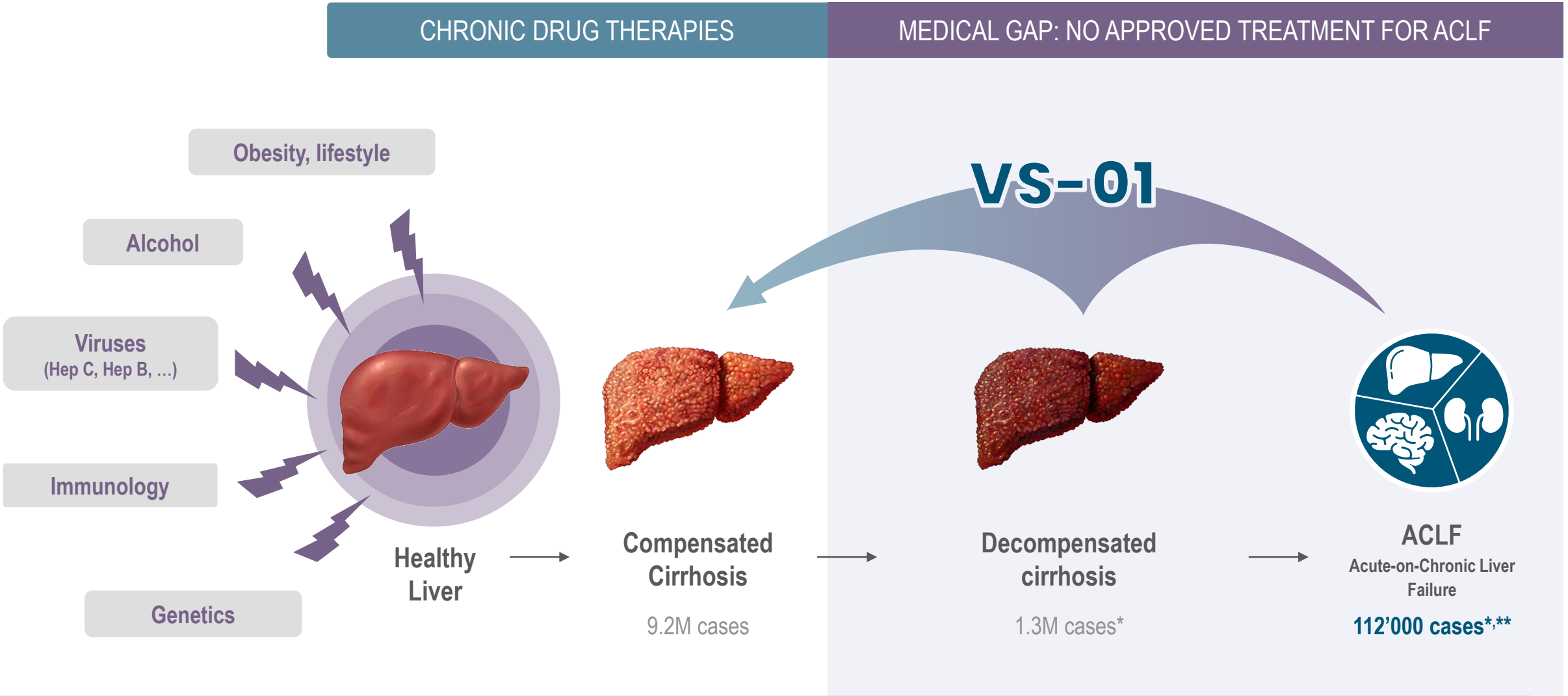
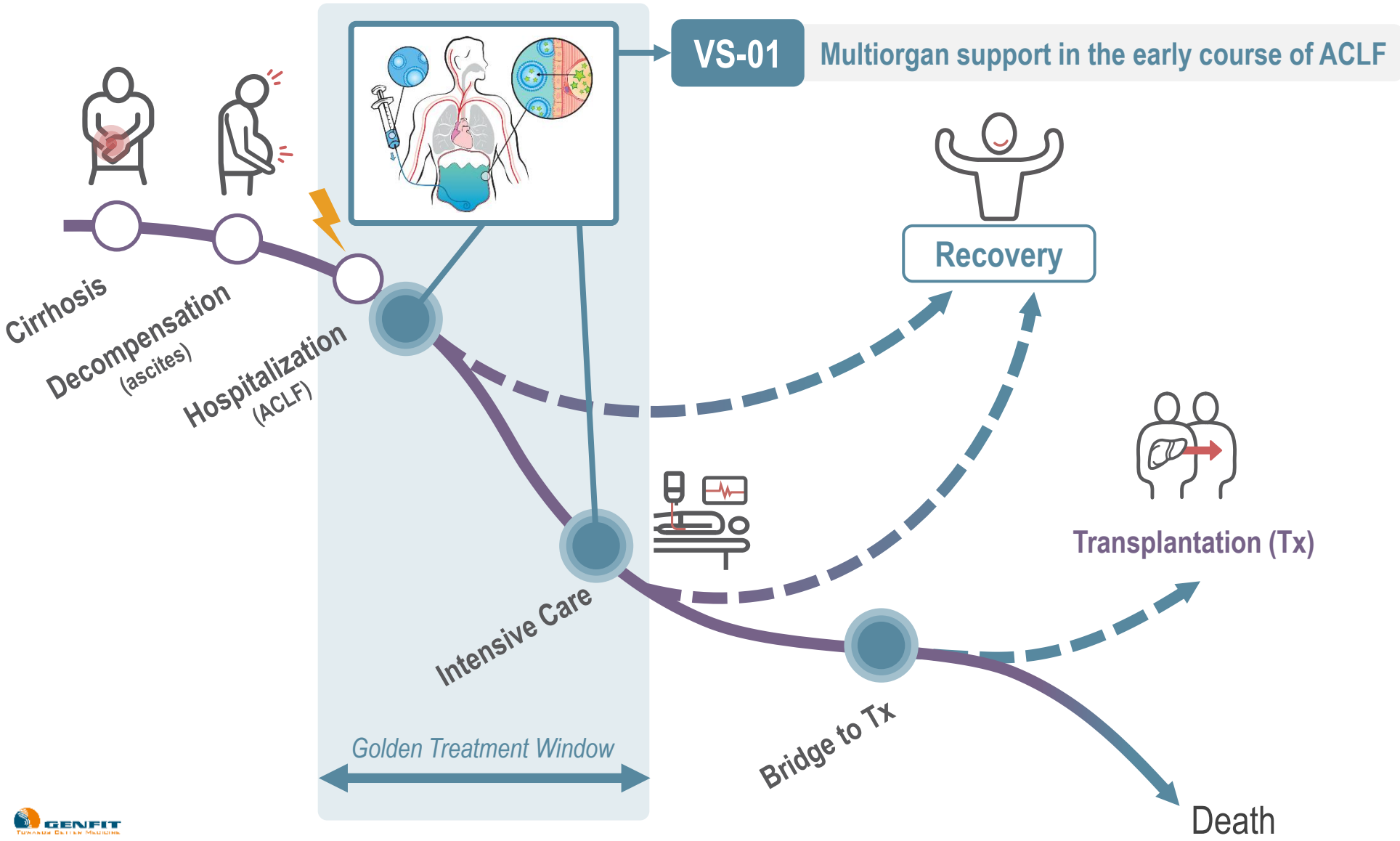
* investigational product that is not approved by any health authority

VS-01 targets timely reversal of ACLF and reduced mortality



*Prevalence US+EU5 of patients with ascites and candidates for VS-01
**Source: third-party US Market Research, December 2021

VS-01 targets first-line treatment of ACLF

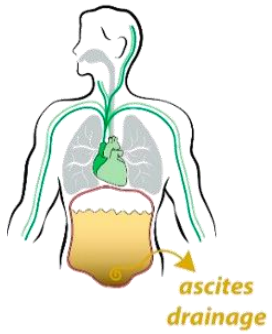


TREATMENT GOALS

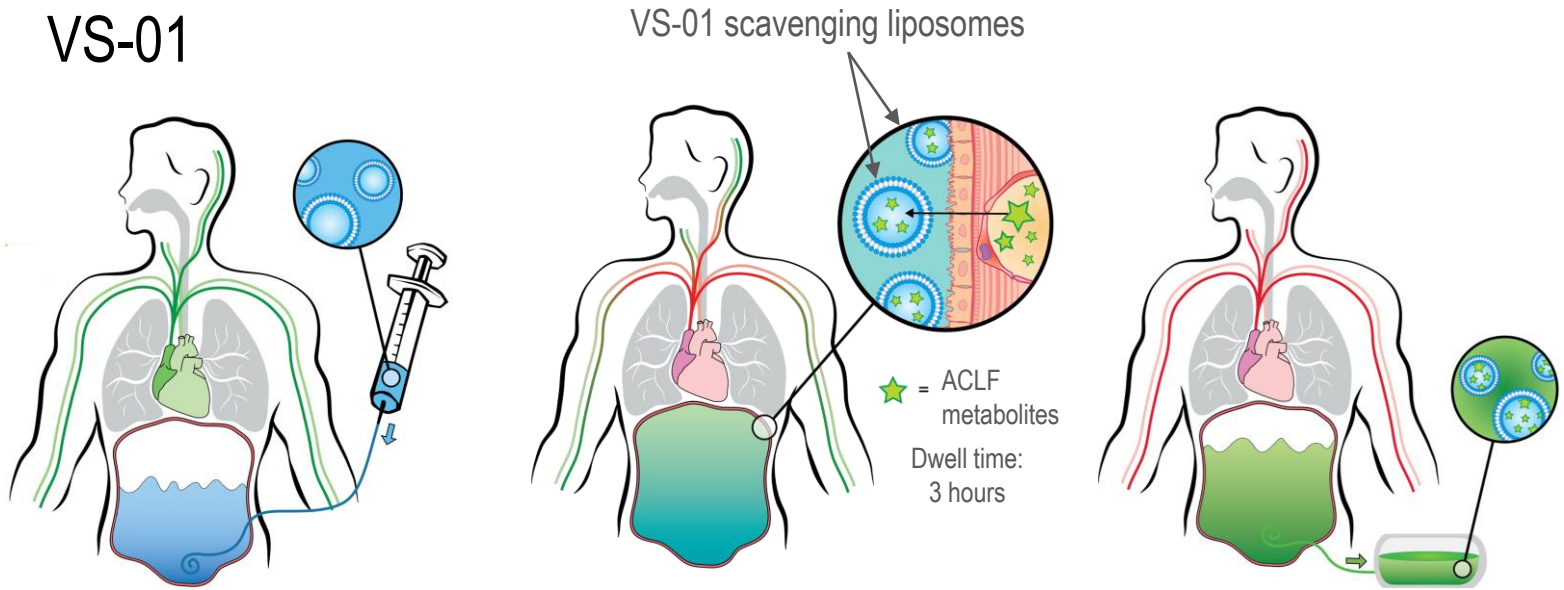
- **R** esolve ACLF
- **I** mprove survival
- **C** hance of liver transplant increased
- **H** ealthcare costs reduced

VS-01 extracts ACLF metabolites failing organs cannot clear

Standard of care
Ascites drainage



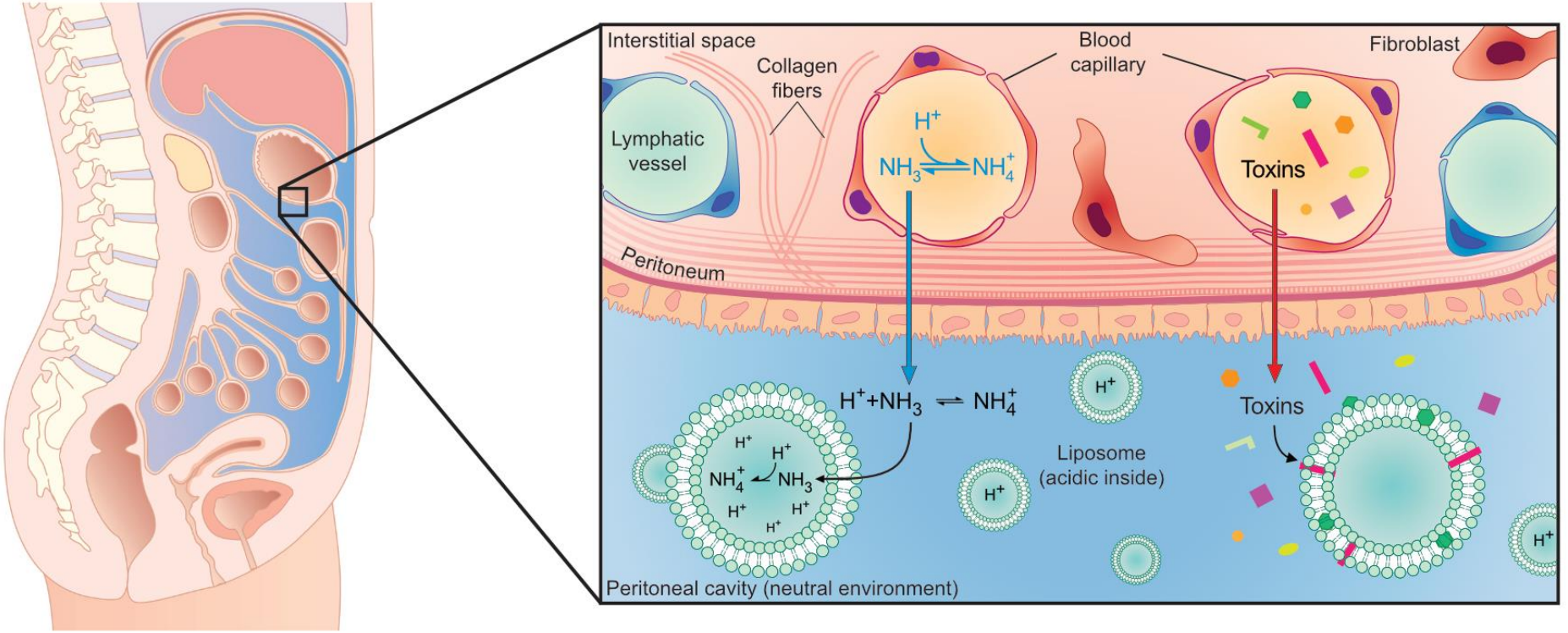
VS-01



Harnesses the intraperitoneal route of administration following paracentesis

- Targets **first-line treatment for ACLF** to **reverse** the disease
- Delivered via **in-place peritoneal access** catheter
- **Treating ACLF early may reduce:**
  - Length of hospital / ICU stay
  - Acute need of transplantation
  - Re-hospitalization
  - Healthcare and hospital costs
- **Favorable safety and tolerability profile** in decompensated cirrhosis as shown in Phase 1b study
- **Targets multiorgan support:** brain, liver, and kidney

VS-01 supports liver, kidneys and brain by clearing toxins from blood to peritoneal space



BRAIN	Specific capture of systemic ammonia into VS-01's liposomes
LIVER	Enhanced hepatic toxins clearance
KIDNEY	Enhanced uremic toxins clearance
INFLAMMATION	Capture of bacterial endotoxins and inflammation mediators

VS-01 mechanism of action

1. UNSPECIFIC BINDING/ADSORPTION

Protein-bound toxins (renal & liver failure):

Shen Y *et al.* J. Liposome Res. 2020

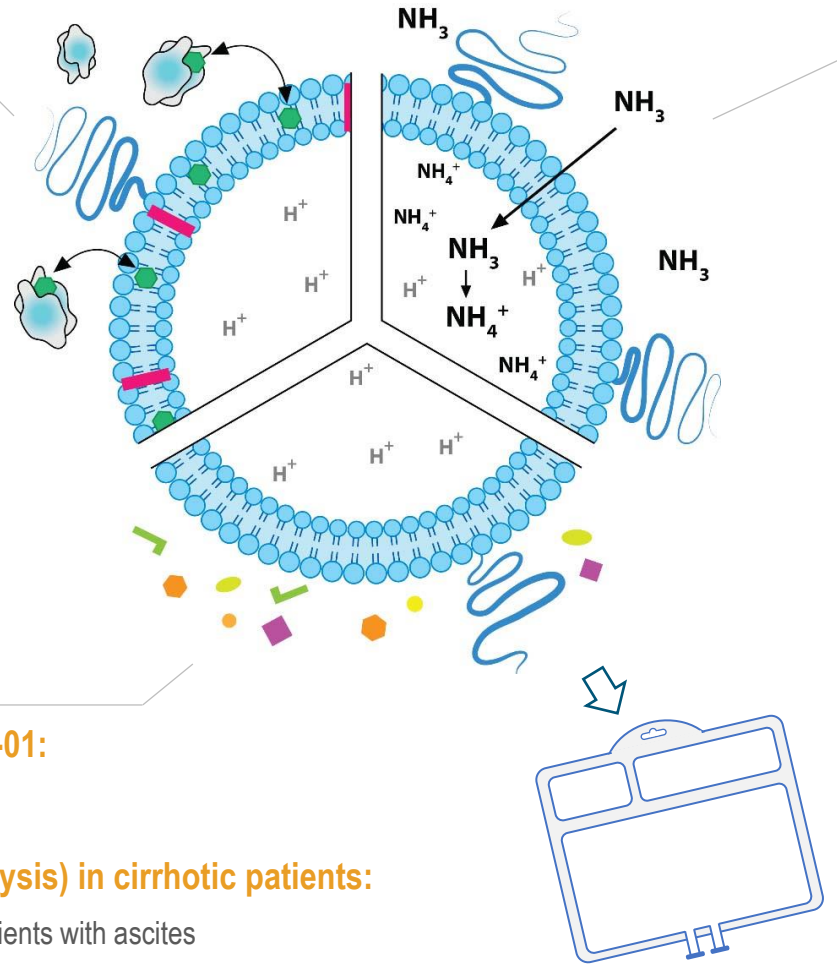
Shi Y *et al.* Perit. Dial Int 2019

Shi Y *et al.* Artif Organs 2018

Bacterial toxins (pneumonia):

Laterre PF *el al.* The Lancet Infect Dis 2019

Henry BD *et al.* Nat Biotech 2014



2. SPECIFIC CAPTURE

Ammonia:

Matoori S *et al.*, J Cont Release 2020

Giacalone G *et al.*, J Cont Release 2018

Agostoni V *et al.*, Adv Funct Mater 2016

Forster V *et al.*, Sci Transl Med 2014

Exogenous toxins (e.g., drugs):

Chapman R *et al.*, J Liposomes Res 2019

Cave G *et al.*, Toxicol Commun 2018

Forster V *et al.*, Sci Transl Med 2014

3. PASSIVE DIFFUSION

Uremic, hepatic, inflammatory toxins removed by VS-01:

Giacalone G. *et al.*, J Cont Release 2018

Safety and benefit of peritoneal dialysis (vs hemodialysis) in cirrhotic patients:

Rajora N *et al.*, Am J Kidney Dis 2021. Review on use of PD in patients with ascites

Nader MA *et al.*, Perit Dial Int 2017. Study on 26'135 patients comparing PD vs HD

Chou C-Y *et al.*, Medicine 2016. Study on 420 patients comparing PD vs HD.

Leading to multiorgan support

VS-01 is safe and efficacious in small and large animal models

EFFICACY

Extraction of **kidney/liver toxins** [3]

- 185 extracted metabolites, including ACLF-related metabolites & uremic toxins

Decrease brain toxicity

- Removes 20x more ammonia than commercial dialysis in rats [1]
- Reduces ammonemia in rats/pigs
- Decrease brain edema in rats [2]

Capture of inflammation mediators

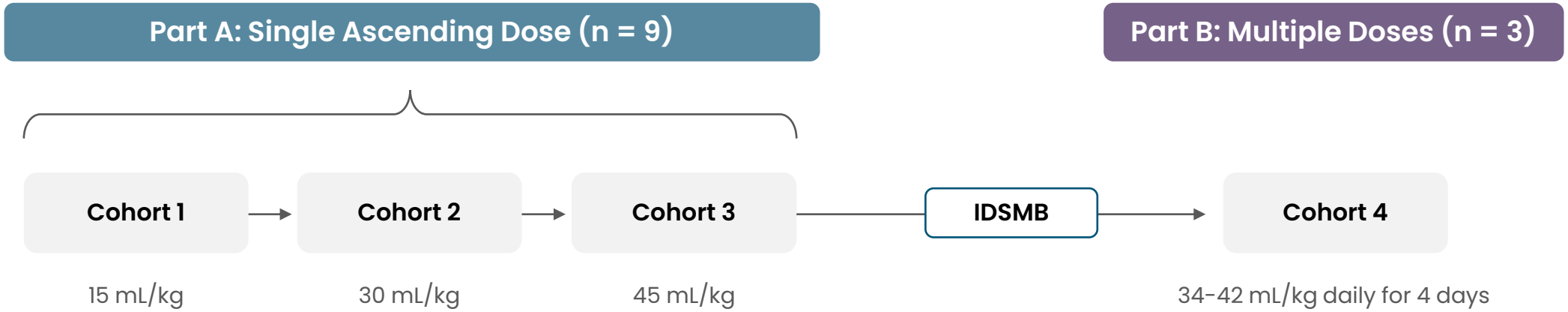
- 28 lipophilic compounds identified, including fatty acids and bile acids [3]

SAFETY

- Safe and well tolerated in healthy and cirrhotic rats during prolonged dwell time >4h [2]
- **No immune reactions + confirmed safety** upon daily injection in healthy pigs for 10 days [2, 4]

[1] Forster V. *et al. Sci Transl Med* 2014, 6:258ra141
[2] Agostoni V. *et al., Adv Funct Mater* 2016
[3] Giacalone G. *et al., J Cont Release* 2018
[4] Matoori S. *et al., J Cont Release 2020*

Phase 1b First-in-Human study: VS-01 on top of SOC



DETAILS

- Study population (n=12):
  - Decompensated liver cirrhosis with
    - Ascites
    - Covert hepatic encephalopathy (minimal HE & HE 1)
- Principal investigator: Prof Dr Jonel Trebicka
- Clinical site: UNIVERSITÄTS KLINIKUM FRANKFURT GOETHE-UNIVERSITÄT

OUTCOME

- ✓ Generally safe and well tolerated
- ✓ Promising preliminary efficacy results
- ✓ Confirmed ease of *i.p.* administration
- ✓ Data selected for Clinical Hepatology Debrief at AASLD 2021

SOC, standard of care | IDSMB, Independent Data and Safety Monitoring Board | HE, hepatic encephalopathy

Phase 1b safety results

- VS-01 was generally safe and well tolerated following single and multiple doses in patients with decompensated cirrhosis
- No SAEs, no deaths, no AEs leading to discontinuation

FAVORABLE SAFETY PROFILE

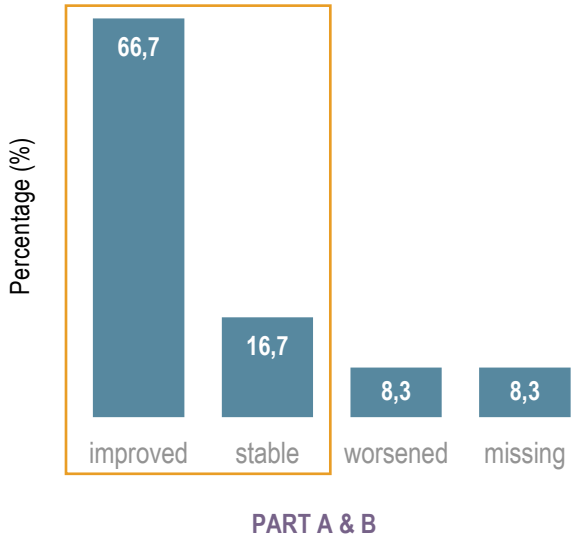
- Citric acid
  - no coagulation dysfunction
- Liposomes
  - no allergic reactions or dyslipidemia
- Administration route of VS-01
  - no infections due to paracentesis catheter (left in situ up to 7 days)
  - stable hemodynamics
- No removal of vital components
  - no salt imbalance
  - no aggravation of malnutrition (albumin)

Phase 1b preliminary efficacy results: liver & brain function

IMPACT ON OVERALL LIVER DISEASE SEVERITY

e.g., assessed by Child-Pugh Score (CPS)

Improved or stable disease: 83.4%

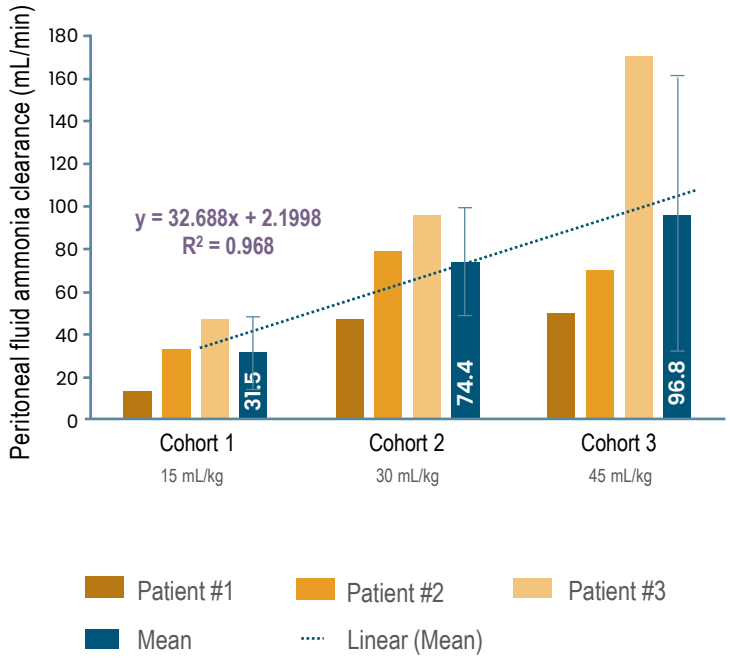


PART A & B

No patients progressed to ACLF

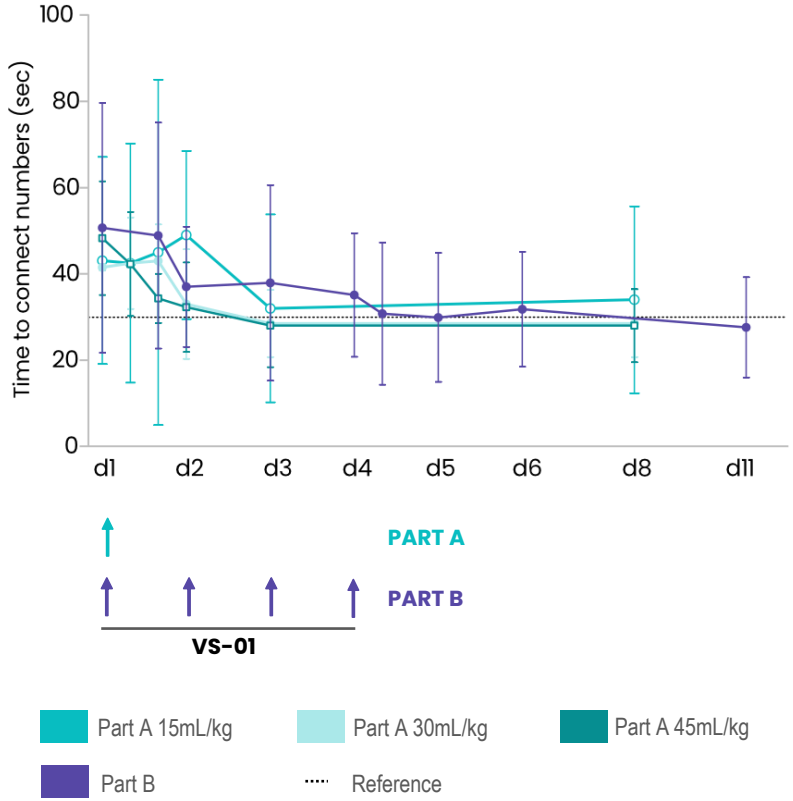
DOSE-DEPENDENT AMMONIA REMOVAL FROM THE BODY

Ammonia clearance increased with VS-01 dosage in peritoneal fluid



IMPROVEMENT IN PSYCHOMETRIC TESTS FOR HE

e.g., number connection test was performed faster

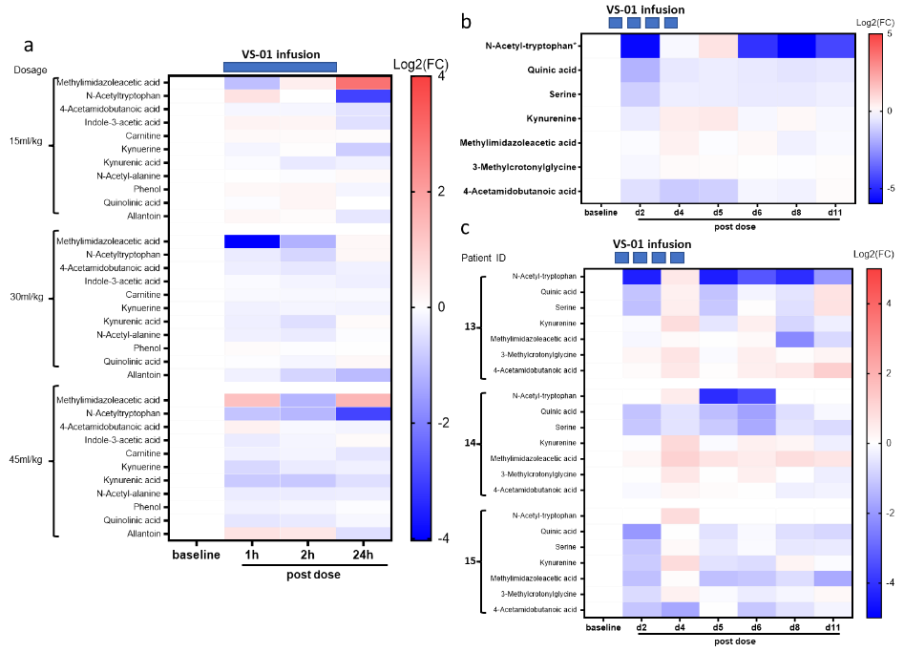


Uschner FE et al, Oral presentation at AASLD 2021, Abstract # 208

Phase 1b preliminary efficacy results: ACLF metabolites & inflammation

REDUCTION OF ACLF METABOLITES[1]

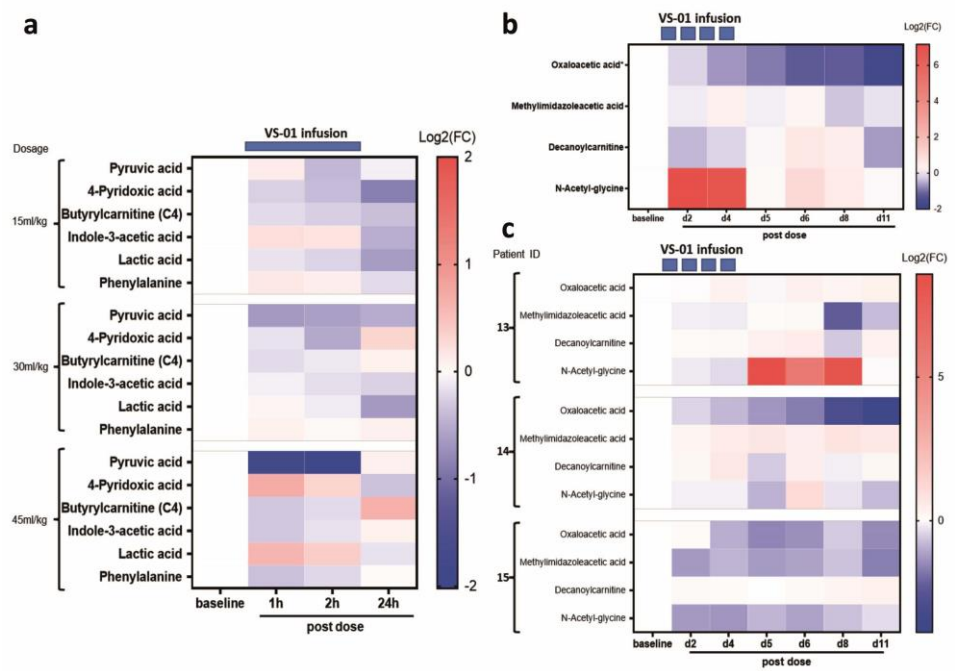
VS-01 reduced plasma metabolites associated with organ failures[2]



- Two abstracts accepted for presentation at EASL-ILC 06/2022
- Abstract selected for 2022 EASL 'Best of International Liver Congress Summit' resource

REDUCTION OF INFECTION-RELATED METABOLITES [1]

VS-01 reduced plasma metabolites associated with bacterial infection[3]



[1]Moreau R et al, Journal of Hepatology 2020 | [2]Uschner FE et al, Poster # 2396 at ILC 2022 | [3]Uschner FE et al, Poster # 2398 at ILC 2022

VS-01 UNVEIL Phase 2 Proof-of-Concept trial

UNVEIL

UN + **VE** + **IL**

UNIQUE

VERSANTIS

INTRAPERITONEAL
LIPOSOMES

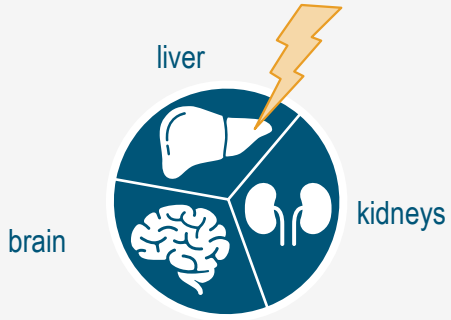
Study title:

A phase 2, **open-label, randomized, controlled**, multi-center, proof of concept study, to assess the **efficacy, safety and tolerability** of VS-01 on top of standard of care, compared to standard of care alone, in adult patients with acute-on-chronic liver failure **(ACLF) grade 1-2 and ascites**

Primary endpoint: CLIF-C ACLF score on Day 7

Target population

ACLF grade 1 & 2



(multi-) organ failure

MULTICENTER STUDY

- Leading EU & US sites and KOLs

KEY SECONDARY ENDPOINTS

- Time to death through Day 28 and 90
- Change in ACLF grade

KEY INCLUSION CRITERIA

- ACLF grade 1-2
- Ascites

KEY EXCLUSION CRITERIA

- Respiratory failure
- Severe circulatory failure
- Uncontrolled severe infection

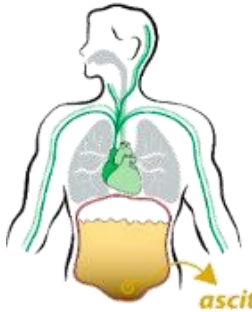
UNVEIL – study design and key endpoints

DAY 0	DAY 1-4	DAY 5-90
SCREENING	RANDOMIZATION (DAY 1)	FOLLOW-UP

N TOTAL = 60 PTS *

Paracentesis

Indwelling catheter

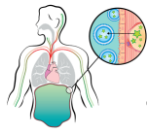


30 PTS

Active treatment group

VS-01 on top of SOC

- *i.p.* administration of VS-01
- 3 hours dwell time
- 4 consecutive days



Day 5-7◆ in-hospital
Day 14, 28, 90: hospital visits
Day 90: EOS

30 PTS

Control group

SOC alone

- *According to international guidelines*

Day 5-7◆ in-hospital
Day 14, 28, 90: hospital visits
Day 90: EOS

* Interim analysis after ≈ 40 pts (H1:2024)
Effect size ≈ 0.80

◆ Primary endpoint:
CLIF-C ACLF score on Day 7

SOC, Standard of Care | ACLF, acute-on-chronic liver failure | HE, hepatic encephalopathy | PTS, patients | i.p., intraperitoneally | EOS, end of study

Acute on-chronic liver failure (ACLF)

GENFIT's programs

VS-01-ACLF*

- *Vincent Forster, PhD, GENFIT, co-founder of VERSANTIS*
- *Prof Katharina Staufer, MD, GENFIT, Chief Medical Officer of VERSANTIS*

NTZ*

- *Dean Hum, PhD, Chief Scientific Officer of GENFIT*
- *Carol Addy, MD, Chief Medical Officer of GENFIT*

* investigational product that is not approved by any health authority

ACLF pathogenesis – NTZ impacts multiple pathways

Precipitating events

Inflammation inducers

Severe systemic inflame-mation

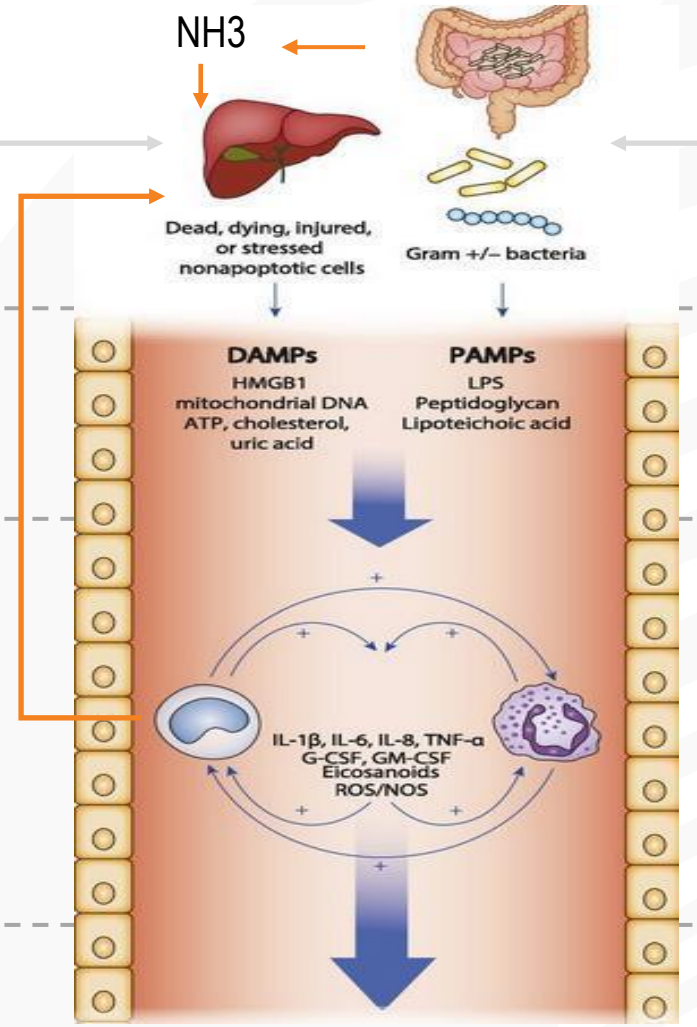
Organ failure

Pathway 1

Cirrhosis/ hepatocyte injury

Pathway 3

Systemic inflammation/ cytokine storm



Pathway 2

Gut Microbiota

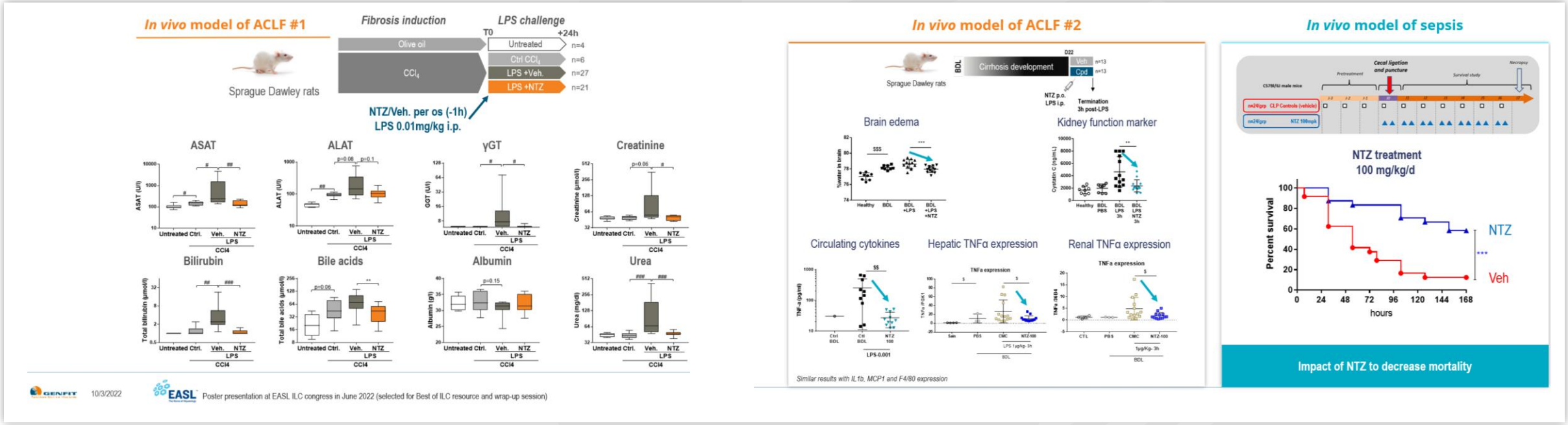
Additional pathways

(e.g. metabolic dysfunction)

Organ failure (kidney, liver, brain, heart, lung)

NTZ preclinical data support ACLF clinical development

1. NTZ **reduces LPS-induced** inflammation in healthy rats*
2. NTZ has **beneficial effects on liver function** markers (bil, alb) in models of cirrhosis*
3. NTZ **reduces brain edema** in models of ACLF (BDL)
4. NTZ **reduces inflammation markers** in models of ACLF (BDL)
5. NTZ **improves survival** in **treatment** models of **Sepsis** (CLP)



10/3/2022 EASL Poster presentation at EASL ILC congress in June 2022 (selected for Best of ILC resource and wrap-up session)

* Poster presentation at the ILC 2022 (London) – EASL
Selected for The Best of ILC resource

NTZ – Ongoing phase 1 studies in subjects with hepatic impairment (HI) and renal impairment (RI)

An Open-label, Phase 1, Multiple-dose Study to Evaluate the Pharmacokinetics and Safety of NTZ 500 mg twice daily for 7 days in Adult Subjects with Moderate & Severe Hepatic Impairment and Adult Healthy Control Subjects

Design

- Moderate to Severe HI subjects vs healthy subjects
- 6-8 Subjects in each group
- Treatment period 7 days
- PK, safety, pharmacodynamics

Healthy control subjects (n=8)

Moderate hepatic impairment (n=8)

Severe hepatic impairment (n=8)

An Open-label, Phase 1, Multiple-dose Study to Evaluate the Pharmacokinetics and Safety of NTZ 500 mg twice daily for 7 days in Adult Subjects with Mild, Moderate & Severe Renal Impairment and Adult Healthy Control Subjects

Design

- Mild, Moderate and Severe RI subjects vs healthy subjects
- 8-10 Subjects in each group
- Treatment period 7 days
- PK and safety

Healthy control subjects (n=7-8)

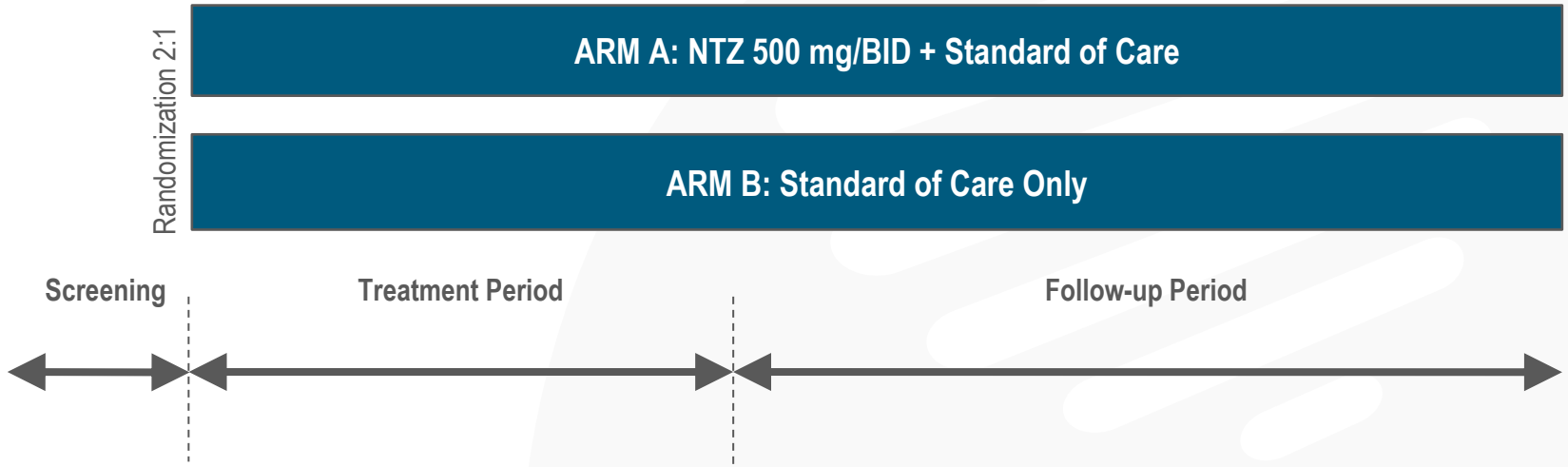
Mild renal impairment (n=7-8)

Moderate renal impairment (n=7-8)

Severe renal impairment (n=7-8)

NTZ – Phase 2a proof-of-concept currently expected to start in 2023

A Multicenter, Randomized, Open-label, Controlled, Phase 2a Clinical Study to Evaluate the Safety, Pharmacokinetics, and Efficacy of Nitazoxanide in Patients with Acute-on-Chronic Liver Failure



Patient Population:

- Patients with ACLF1 or ACLF2
- ACLF 1 may be outpatient or hospital inpatient

Objectives:

- To evaluate NTZ safety in patient with ACLF
- To evaluate NTZ PK in patients with ACLF
- To evaluate NTZ clinical outcomes in patients with ACLF
- To evaluate NTZ pharmacodynamics in patients with ACLF

Short Q&A (10 minutes)

Questions?

Acute on-chronic liver failure (ACLF)

Market opportunity

- *Stephan Gauldie, PhD, Managing Director, Strategy Consulting at Back Bay Life Science Advisors*
- *Mavra Nasir, PhD, Senior Consultant, Strategy Consulting at Back Bay Life Science Advisors*

Back Bay led a US-focused market assessment of acute-on-chronic liver failure (ACLF) for VS-01 between November 2021 – December 2021

Project Objectives

Key components of the analysis included (but not limited to):

- The degree of unmet need in ACLF, as defined by the literature and hepatologists, including epidemiological review, and definition of key segments
- Pressure testing and refining the perspective on the ACLF addressable market, US payer feedback, and hepatologist expectations regarding VS-01 positioning

We added an EU4+UK focused total addressable market assessment based on secondary research for this presentation

Sources: Back Bay analysis

Our evaluation included an extensive review of published literature, ten in-depth discussions with key opinion leaders (KOLs) managing patients with ACLF, two hospital pharmacists, two hospital administrators, and one MCO payer in the US

Research Methodology

Primary Literature and Syndicated Reports

- PubMed/peer reviewed clinical and scientific literature
- Non-proprietary elements of previous Back Bay engagements
- Relevant databases
- Relevant market reports and publications
- Conference proceedings
- Materials provided by Versantis

Interviews

- In-depth discussions with 10 key opinion leaders:
  - Hepatologists and intensivists had both research (clinical or basic) responsibilities and clinical practices as well as experience managing patients with ACLF
  - Hospital-based payers included pharmacists and administrators with direct experience managing hospital budget, formulary, and billing decisions

Stakeholder	Completed
Hepatologist	7
Intensivist	3
Hospital Pharmacist	2
Hospital Payer	2
MCO Payer	1

Our model comprises senior-level staff with substantial research and domain-area expertise that are able to create an environment that allows for in-depth discussions within this setting, rather than the typical “script” or “survey” based approach

Sources: Back Bay analysis, MCO: managed care organization

Given the lack of approved treatments, high in-patient mortality, and the significant cost associated with hospitalization, there is a huge unmet need for efficacious therapies for ACLF

Mortality by Grade, ACLF		
ACLF grade (EASL-CLIF)	Day 28	Day 90
Grade 1	23%	41%
Grade 2	31%	55%
Grade 3	75%	78%

Mortality

Economic Burden of Chronic Diseases, 2010 (Table 4: Allen et al Hepatology, 2016)				
Chronic Disease	#hospitalizations	LOS (Days)	Inpatient Mortality	Mean Cost Per Hospitalization
Pneumonia	1.1M	5	3.3%	$7,581
Congestive heart disease	1.0M	5	3.0%	$8,315
Cerebrovascular disease	1.0M	6	4.7%	$8,117
Septicemia	808,000	9	16.3%	$15,467
Cirrhosis	606,288	7	7.5%	$15,732
ACLF	**28,637**	**16**	**53.3%**	**$54,727**

- **There are no FDA approved treatments for ACLF, and short-term mortality can range from 23-75% depending on ACLF grade**
- **Compared to other chronic diseases managed in the in-patient setting, management of ACLF represents a substantial economic burden**
  - **In 2010, the cost per hospitalization for ACLF was 3.5x higher than cirrhosis ($54,727 versus $15,732)**

LOS: length of hospital stay

Sources: BBLSA prior work, BBLSA physician interviews (n = 10), Arroyo V et al 2016 Nature Review Disease Primers 2, 16041, Allen et al Hepatology. 2016 Dec;64(6):2165-2172

The greatest unmet need in the treatment of ACLF is lack of available therapies that can prevent disease progression and reduce mortality

1 Targeted treatments to prevent progression and reduce mortality

There is a high unmet need to reverse or slow down the course of ACLF

- The care of ACLF patients is resource intensive, with hospital stays of ~13-16 days
- With a lack of available therapies, the progression of ACLF can be rapid and quickly render patients too sick to be eligible for transplant
- Due to the serious complications that arise from systemic inflammation in ACLF, **treatments that can address the underlying systemic inflammation are highly desirable**

*"If the liver is not completely fibrotic, **any treatment that can give the liver a little bit of time to recover** from acute insult would be good"* – US Intensivist

2 Generalizing definitions & developing evidence-based guidelines

There is a need to simplify definitions to improve generalizability

- Educating physicians about ACLF especially in non-academic settings and understanding the burden of ACLF in transplant and non-transplant centers was also cited as key area of future research
- While some prognostic metrics have been used to identify patients at high risk for mortality (e.g., CLIF- C ACLF score), their use has yet to become standardized and **physicians are seeking markers that can predict onset of ACLF**

*"Physicians don't really assign a grade to a patient, **you know how sick someone is based on how many organs are failing**"* – US Hepatologist

3 Prevention of insult & organ failures

Better understanding of the pathogenesis of ACLF to prevent onset

- Understanding the disease pathophysiology remains an active but nascent area of research
- Researchers are evaluating the use of serum, urine metabolomics and stool microbiome from cirrhotic patients with acute decompensation ± ACLF to identify a prognostic fingerprint

*"It would be **ideal to be able to prevent ACLF or predict who is at high-risk of developing ACLF rather than diagnosing**"* – US Hepatologist Intensivist

Sources: BBLSA prior work, BBLSA physician interviews (n = 10), Bajaj et al Clin Gastroenterol Hepatol. 2019;17(4):756-765.e3, Bajaj et al Hepatology. 2021;74(5):2699-2713, Moreau et al J Hepatol. 2020;72(4):688-701, Chen et al .J Gastroenterol Hepatol. 2015;30(9):1429-1437

There are currently three therapies in active clinical development for ACLF in the US, with one agent (plasma exchange with human serum albumin/Grifols) in pivotal trials

Mechanism	Product, Company	Status	RoA	Patient population	Trial Design
Plasma exchange with human serum albumin 5%	human serum albumin 5% GRIFOLS	Ph 3 ongoing	IV	ACLF-1b ACLF-2 ACLF-3a	• **NCT03702920 (APACHE):** Open label, albumin 5% vs SMT • **Primary endpoint**: Time to death through day 90 • **Expected enrollment**: 380 participants – as of April 2021, 90 (29%) of participants had been randomized • **Est. primary completion date**: Oct 2026
Human allogeneic liver-derived progenitor cell therapy	HepaStem® Cellaïon	Ph 2b ongoing	IV	ACLF 1 ACLF 2	• **NCT04229901 (DHELIVER):** double-blinded, randomized placebo-controlled • **Primary endpoint:** Overall survival proportion 90 days post-first infusion • **Expected enrollment:** 363 participants • **Est. primary completion date:** Jan 2023 • Expected approval (company deck): 2027
Toll-like receptor 4 antagonist	Resatorvid (TAK-242) AKAZA BIOSCIENCE	Ph 2 preparation ongoing	IV	ACLF 1 ACLF 2	• Not yet listed on clinicaltrials.gov • Company website indicates preparations for a randomized, double-blind, placebo-controlled pan-European study are underway • 28-day survival rates and changes in key biomarkers are listed as key endpoints
RoA: route of administration, IV: intravenous, SMT: standard medical treatment					

VS-01 was viewed as a complementary approach to the above therapies given its MoA, positioning (ACLF grade 1 and 2 pts with ascites), and differentiated RoA (complementary to integration with current workflow)

Sources: BBLSA physician interviews (n = 10), TrialTrove, clincaltrials.gov, Company websites, Press releases

Based on our conservative estimates, the current total addressable market for ACLF is ~215K across the US and EU4+UK and is expected to grow to ~300K by 2036

2022 Estimates

Prevalent Population

110/100k[2,3] , YoY increase: 2%[1,4]

Decompensated cirrhosis-related hospitalization

721K (363K US, 358K EU4+UK)

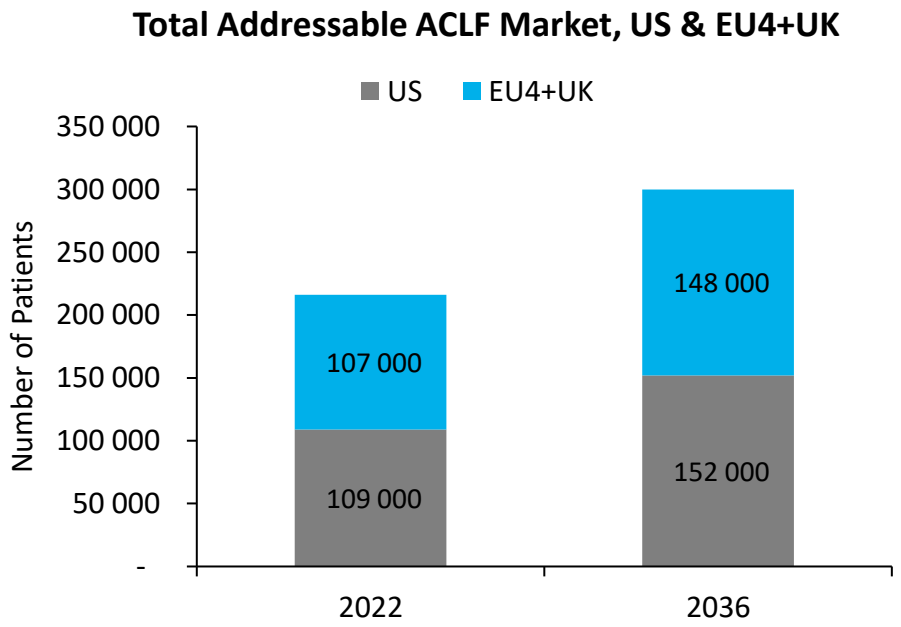
30%[5-7]

Patients with ACLF

216K pts with ACLF (109K US, 107K EU4+UK)

EASL-CLIF

45%[1]	*35%[1]*	*20%[1]*
ACLF grade 1	ACLF grade 2	ACLF grade 3
97K	76K	43K



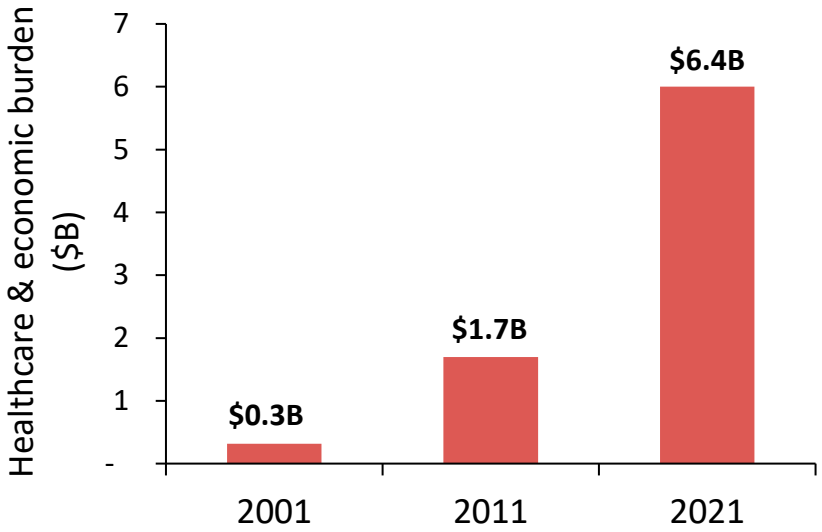
Key Considerations

- Growth in total addressable ACLF market is driven by increase in liver cirrhosis rates due to increasing prevalence of alcoholic liver disease, nonalcoholic fatty liver disease and hepatocellular cancer
- EU4+UK estimates are conservative and based on US data – potential for a larger addressable patient pool in key European markets given data from the GBD 2017 cirrhosis study[2] indicates an average decompensated cirrhosis related hospitalization rate of 175/100k across Germany, Spain, Italy, France and UK

Sources: 1) BBLSA physician interviews (n = 10), 2) GBD 2017 cirrhosis collaborators, Lancet Gastroenterol Hepatol. 2020 Mar;5(3):245-266 (supplementary appendix table 5), 3) Desai et al, Clin Transl Gastroenterol. 2019 Jul;10(7):e00062, 4) Hirode et al JAMA Netw Open. 2020 Apr; 3(4): e201997, 5) Hernaez et al, J Hepatol. 2019 Apr;70(4):639-647, 6) Mezzano et al, Gut 2022 Jan;71(1):148-155, 7) Moreau et al, Gastroenterology. 2013 Jun;144(7):1426-37, 1437.e1-9.

ACLF represents a clear and growing economic burden; hospitals bear a large proportion of patient costs and are looking for ways to expand reimbursement and reduce costs, particularly the number of patients requiring high-intensity care

ACLF Economic Burden[1] ($), US



ACLF represents a large health care and economic burden in the US

- Cost to the system grew 5-fold from 2001-2011 and nearly 4-fold during 2011-2021

Reimbursement and payer dynamics mean hospitals bear a significant proportion of treatment expense

- Institutions are actively looking for ways to improve reimbursement and cut costs for ACLF patients

Variable reimbursement from private payers

- Hospitals are typically reimbursed ~$10k-$17k for Medicare ACLF patients and $50k-$75k for privately insured ACLF patients
- Reducing escalation to higher intensity care is key to cost containment as ICU beds can cost ~$6-$7k more per night and rapidly erodes DRG margins

Hospitals are pushing for fee-for-service agreements with private payers for enhanced reimbursement

- Institutions can receive $80k-90k for privately insured ACLF patients; represents a significant profit over patients with bundled payment
- Hospitals will receive additional reimbursement beyond the agreed upon DRG bundled payment for products that receive NTAP status

*"I would say **we are taking a loss on Medicaid, breaking even on Medicare, and making a 20-30% profit on privately insured patients**"* – US Hospital Payer

*"At my institution **ACLF patients would fall under a fee-for-service agreement for private payers**. The payer would pay a base facility fee of $37k-$45k and additional fees per procedure"* – US Hospital Payer

Sources: 1) Allen et al Hepatology. 2016 Dec;64(6):2165-2172; 2021 estimate extrapolated based on mean hospitalization cost applied to 2021 estimated patient population; KOL and hospital payer interviews

Overall, experts were optimistic with the VS-01 profile, and particularly liked the ease of administration and the potential to eliminate pro-inflammatory metabolites

	Base Case	Best Case
Primary endpoint	• Improvement of HE by at least 1 grade or recovery from overt HE	• Change from baseline in mean CLIF-C ACLF score on Day 7 (a 4-point difference in CLIF-C-ACLF between arms is assumed to correspond to a 10% difference in mortality at Day 28) • Effect on mortality on Day 28
Secondary endpoint(s)	• Safety and tolerability of Product X in ACLF patients • Additional ACLF parameters such as change from baseline in mean CLIF-C ACLF score on Day 5, evolution of ACLF grade from baseline to Day 5 and Day 7, effect on organ dysfunction using the CLIF-SOFA score, effect on organ failure using the CLIF-C OF score and effects on Child Pugh, MELD, and MELD-Na scores • Effect on HE will be assessed by West Haven criteria, Glasgow Coma Scale, Animal Naming Test, Psychometric Hepatic Encephalopathy Score (PHES), and Stroop Test	
Key exploratory endpoint(s)	• Effect on circulation and lung failure/dysfunction • Effect on renal function and liver function • Effect on serum inflammatory biomarkers, serum CRP, procalcitonin and plasma lactate • Effect on duration of hospitalization and/or stay in ICU • Effect on hospital readmission rate • Effect on in-hospital / ICU mortality up to Days 14, 28 and 90 • Effect on transplant-free survival up to Days 14, 28 and 90	

VS-01 Feedback

*"If you can address and remove the inflammatory markers of ACLF, you are not only **addressing the pathophysiology of ACLF, but also the physiology of ammonia production** – both of which are positive"* – US Hepatologist

*"The **motivation to enroll patients in a trial with this product would be high**, as this is a high-risk population"* – US Hepatologist

*"**This is much more attractive to me** than the use of extracorporeal dialysis machines"* – US Hepatologist

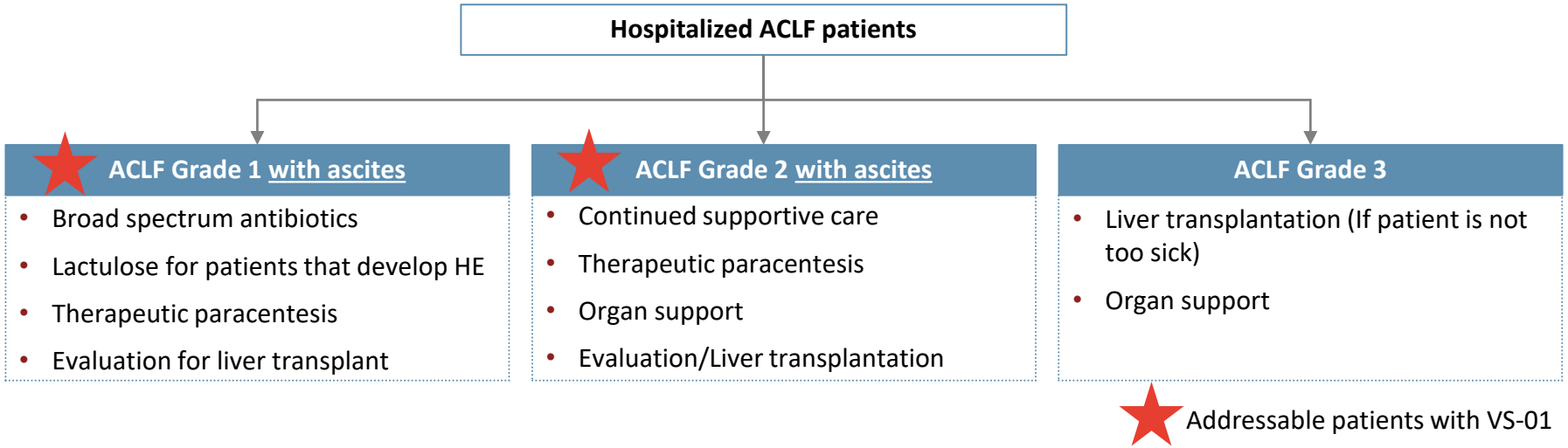
*"I know **some people will have an issue with an indwelling catheter**, but I have left catheters in the peritoneum before, and **I don't think it is harmful if done correctly**"* – US Hepatologist

*"It would be like **an explosion went off if you could prove mortality benefit**. But, if you can improve ACLF score for a proof of concept trial, that is pretty good"* – US Hepatologist

*"Wow, this is pretty cool. I guess it is sort of like peritoneal dialysis. With the right training and precautions, **doing this sterilely shouldn't be a problem**"* – US Intensivist

Sources: 1) BBLSA physician interviews (n = 10)

Physicians would use VS-01 in patients with ACLF Grade 1 and 2 who have ascites in conjunction with standard of care



VS-01 Positioning Considerations

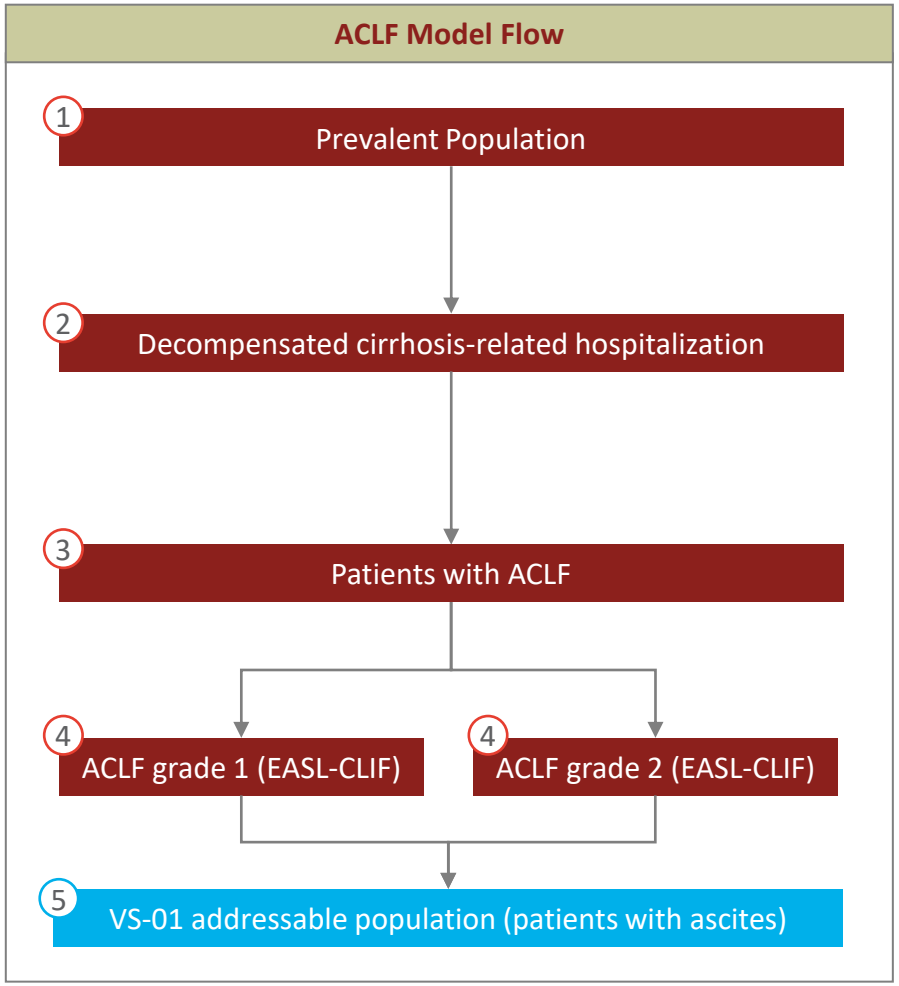
Given that the peritoneal drainage traditionally occurs with 24-48 of hospital admittance, VS-01 would likely be initiated early in the treatment course of ACLF

- With the lack of available treatments for ACLF, physicians indicated that they would be interested in using VS-01 to prevent possible disease progression of ACLF
- Experts would use VS-01 concurrently with standard medical treatment
- Integration into workflow was not cited as a major barrier - the preferred indwelling catheter for paracentesis (commonly referred to as a "pig tail catheter") would most likely be implanted by an interventional radiologist

HE: hepatic encephalopathy
Sources: BBLSA prior work, BBLSA physician interviews (n = 10)

ACLF

The current addressable market for VS-01 if targeting ACLF grade 1 and 2 patients presenting with ascites is ~130K across the US and EU4+UK



	Variable	Assumptions	Rationale & Source(s)
1	Prevalent population	• US: 330M; YoY growth: 0.4% • EU4+UK: 325M; YoY growth: 0.3%	• US census data • EU country specific census data
2	Hospitalization due to decompensated cirrhosis, per 100k	• Average (range): 110/100k (105/100k-113/100k) • YoY increase: Base: 2%, Upside: 5%	• GBD 2017 cirrhosis collaborators, Lancet Gastroenterol Hepatol. 2020 Mar;5(3):245-266 (supplementary appendix table 5) • Desai et al, Clin Transl Gastroenterol. 2019 Jul;10(7):e00062 • Hirode et al JAMA Netw Open. 2020 Apr; 3(4): e201997
3	ACLF prevalence (%)	• Average (range): 30% (26-35%)	• Hernaez et al, J Hepatol. 2019 Apr;70(4):639-647 • Mezzano et al, Gut 2022 Jan;71(1):148-155 • Moreau et al, Gastroenterology. 2013 Jun;144(7):1426-37, 1437.e1-9.
4	ACLF grade 1 and 2 (%)	• ACLF grade 1: 45% (40-50%) • ACLF grade 2: 35% (30-40%)	• KOL feedback • Hernaez et al, J Hepatol. 2019 Apr;70(4):639-647 • Gustot et al Hepatology. 2015 Jul;62(1):243-52
5	ACLF grade 1 and 2 pts with ascites (%)	• Ascites prevalence: 75% (60-90%)	• KOL feedback

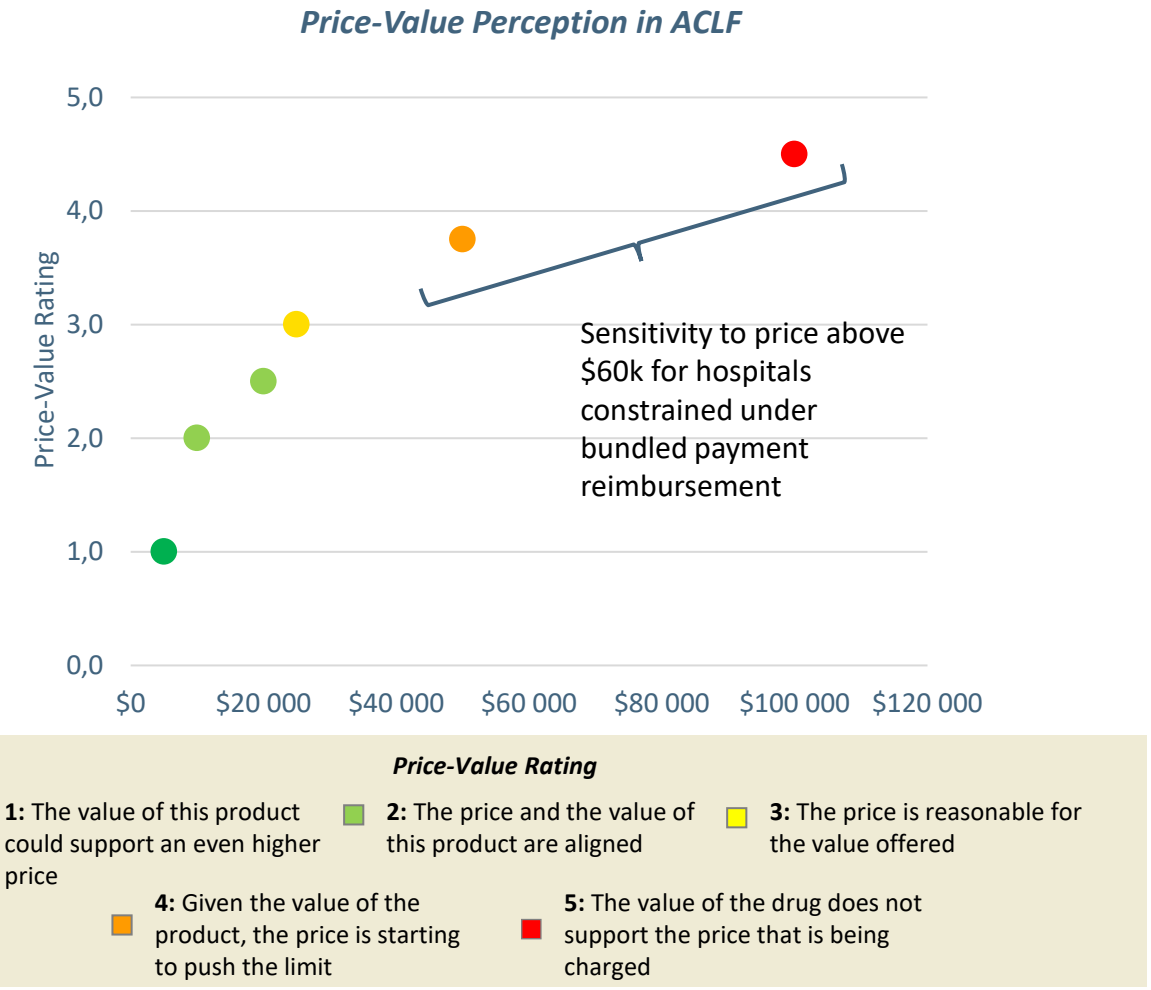
Sources: Back Bay analysis

Hospital pharmacists and administrators appreciated that VS-01 addresses a patient population with high unmet need and could provide additional cost-savings

Topic	*Key Considerations*	*Quotes*
Target Population	**Payers understand that ACLF patients have high unmet treatment needs and are generally unprofitable due to extended length of stays and intensive level of care** • Treating ACLF Grade 1 and 2 patients early with VS-01 to slow disease progression, reduce overall length of stay, and reduce number of ICU admissions is very attractive to hospital payers	*"It seems like this product would have significant demand* ***– based on what I have seen, this is an ideal patient population to target"*** – US Hospital Payer
Workflow Considerations	**No significant changes to workflow are needed to accommodate VS-01** • Some hospitals may require the use of a high-level procedure room for the administration of VS-01 due to concerns of sterility • An added step in patient workflow will likely be scheduling an interventional radiologist to place the indwelling catheter by ultrasound prior to paracentesis and subsequent administration of VS-01	*"We would look at this as a* ***procedure event*** *– the patient would be in paracentesis procedure room and then pharmacy would receive the order and not start preparing until the doctor confirms they are ready for procedure" – US Hospital Payer*
HEOR Metrics	**Hospital payers will be focused on VS-01's impact on length of stay, time in ICU, and readmission rates** • Hospitals will continuously collect and monitor data on utilization of the product and likely reevaluate VS-01 ~12-24 months after adoption • Early demonstration of reduction in LOS and ICU admissions in clinical trials will have a positive impact on early adoption of VS-01	*"When evaluating a new drug,* ***we do routinely look at the current average stay cost compared with the cost of the novel therapy"*** – US Hospital Payer

Sources: 1) BBLSA payer interviews (n = 4)

Payers view a treatment cost in the range of ~$30-$50k per patient to be reasonable given the high level of unmet need and extended hospital stays



Key Takeaways

Payers acknowledged that the target patient population has little treatment and there is a high potential for significant cost savings on reduced ICU admissions and length of hospital stay

- Payers were wary of treatment prices **greater than $60k**, unless **significant reduction in healthcare resource utilization is demonstrated for this patient population**. Additional positive **clinical data** and exploratory endpoints (**lengths of stay**, **readmissions rate**, **mortality**, etc.) could help justify **a higher price**
- Without that data, substantial restrictions would likely be placed for any therapy above $60k, for example restricted to use by hepatologist attending physician or after failure of other cheaper symptom management options

Sources: 1) BBLSA payer interviews (n = 4)

Short Q&A (10 minutes)

Questions?

Hepatic encephalopathy (HE)

Disease state

- *Jennifer C. Lai, MD, MBA, Transplant hepatologist, University of California, San Francisco (UCSF), USA – Endowed Professorship of Liver Health & Transplantation*

Hepatic encephalopathy (HE)

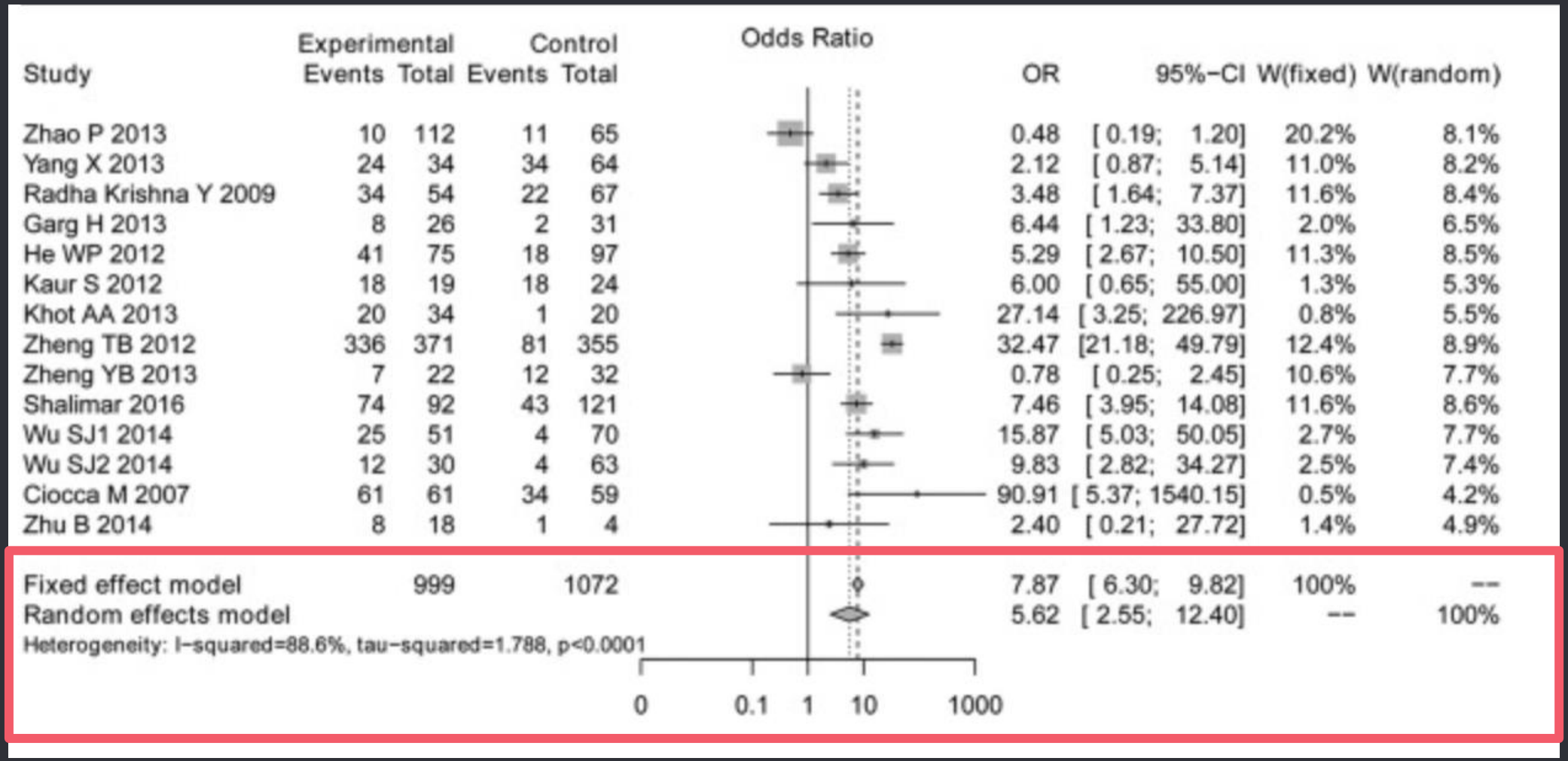
Jennifer C. Lai, MD, MBA
Transplant Hepatologist
Endowed Professor of Liver Health & Transplantation
University of California, San Francisco (UCSF)

Hepatic encephalopathy

- One of the major complications of advanced liver disease and portal hypertension
  - 30-40% of patients with cirrhosis will experience at least 1 episode
- Represents a diverse spectrum of neurologic, psychiatric, and musculoskeletal symptoms
  - Sleep-wake cycle disturbance
  - Fatigue
  - Concentration difficulty
  - Personality changes – apathy, irritability, disinhibition
  - Tremor
  - Cognitive deficits – disorientation, memory loss, slurred speech, confusion
  - Coma

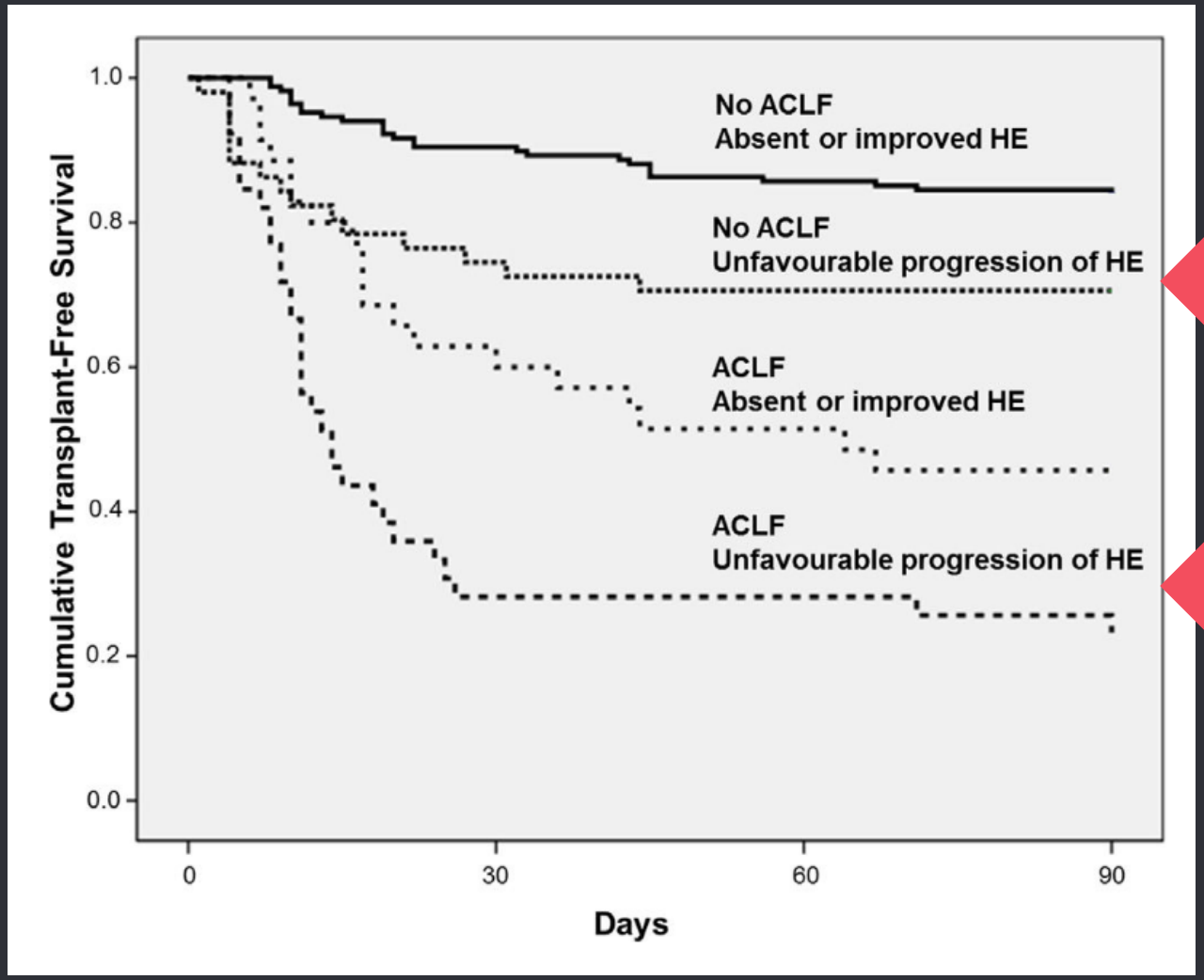
Elsaid MI, Rustgi V. Clin Liver Dis 2020. Kabaria S, *et al.* EMJ Hepatol 2021.

HE → death



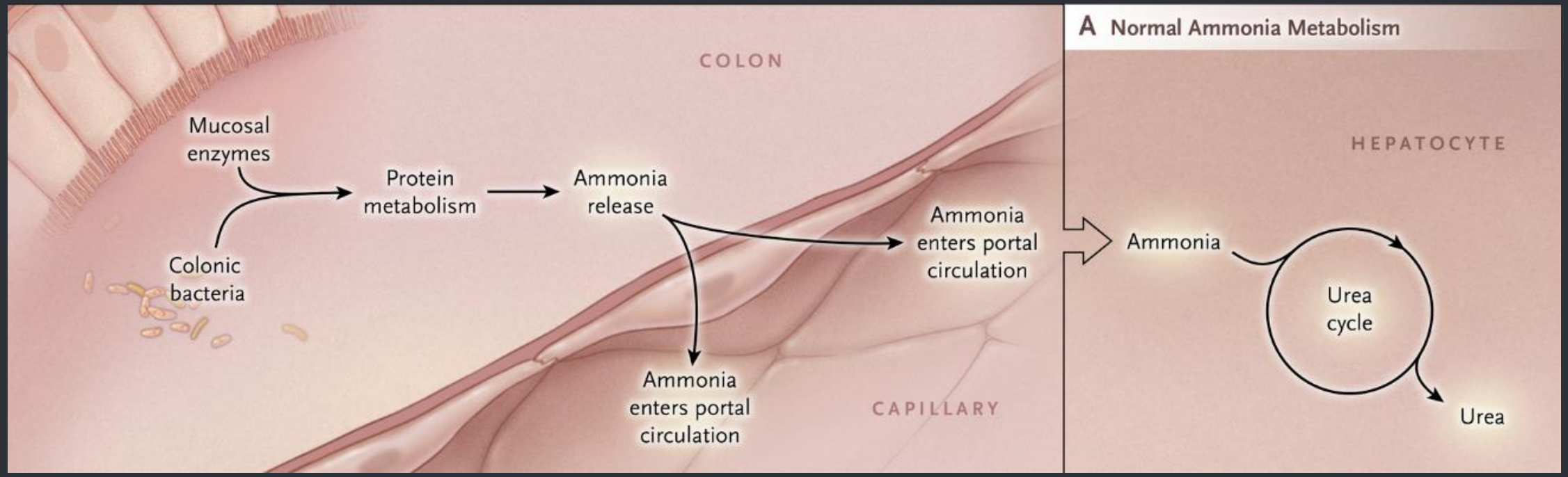
Yu H, *et al*. Ann Hep 2019.

Increased risk of death in ACLF



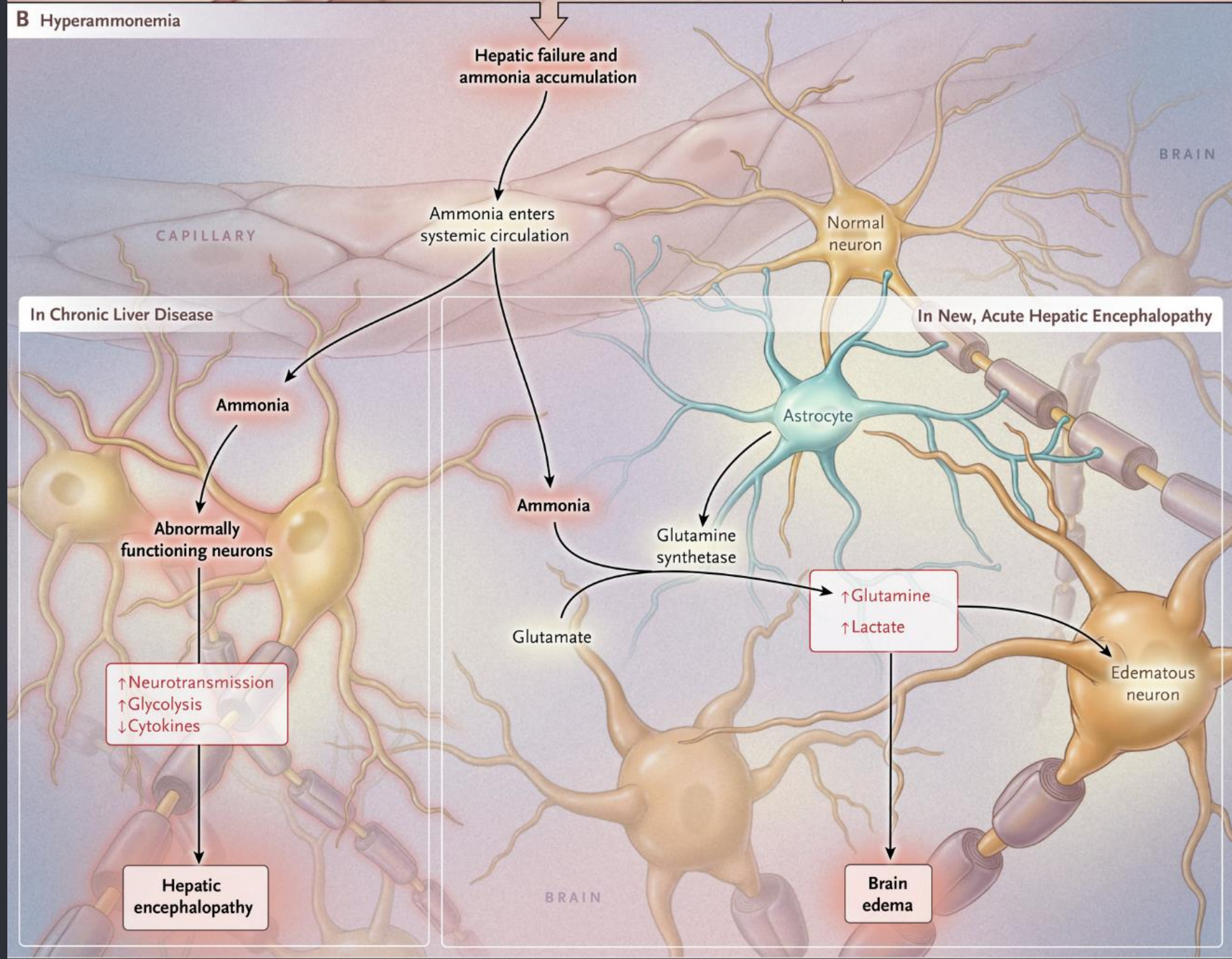
Maggi DC, *et al*. Ann Hep 2019.

Ammonia clearance (normal liver function)



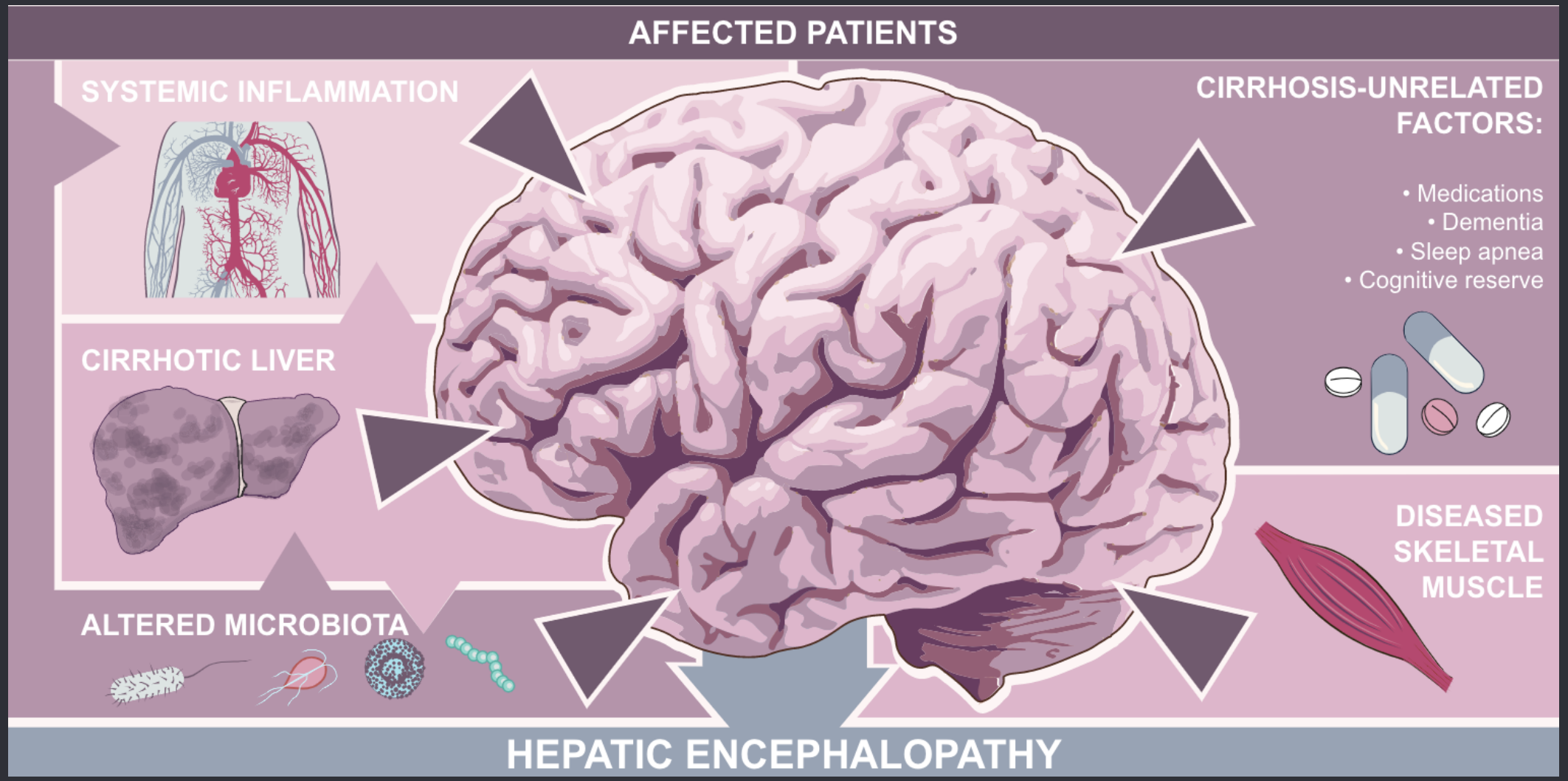
Widjicks E. NEJM 2016.

Hyper-ammo-nemia (abnormal liver function)



Widjicks E. NEJM 2016.

Multi-factorial etiology

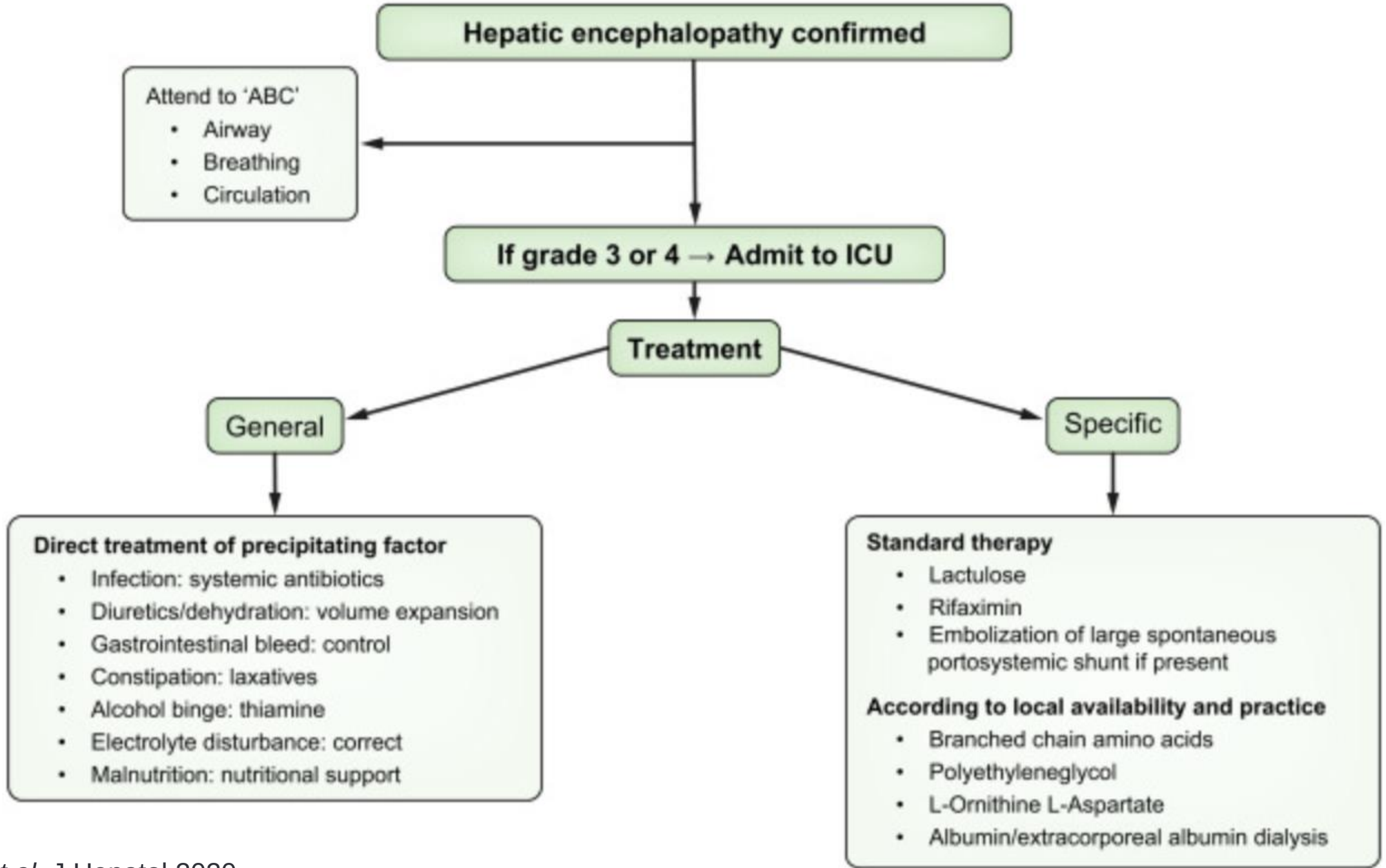


Bajaj J. J Hep 2018.

Classification

WHC Including MHE	ISHEN	Description	Suggested Operative Criteria
Unimpaired		No encephalopathy at all, no history of HE	Tested and proved to be normal
Minimal	Covert	Psychometric or neuropsychological alterations of tests exploring psychomotor speed/executive functions or neurophysiological alterations without clinical evidence of mental change	Abnormal results of established psychometric or neuropsychological tests without clinical manifestations
Grade I	Covert	• Trivial lack of awareness • Euphoria or anxiety • Shortened attention span • Impairment of addition or subtraction • Altered sleep rhythm	Despite oriented in time and space (see below), the patient appears to have some cognitive/behavioral decay with respect to his or her standard on clinical examination or to the caregivers
Grade II	Overt	• Lethargy or apathy • Disorientation for time • Obvious personality change • Inappropriate behavior • Dyspraxia • Asterixis	Disoriented for time (at least three of the followings are wrong: day of the month, day of the week, month, season, or year) ± the other mentioned symptoms
Grade III	Overt	• Somnolence to semistupor • Responsive to stimuli • Confused • Gross disorientation • Bizarre behavior	Disoriented also for space (at least three of the following wrongly reported: country, state [or region], city, or place) ± the other mentioned symptoms
Grade IV	Overt	Coma	Does not respond even to painful stimuli

Vilstrup H, *et al*. Hepatol 2014.



Rose CF, *et al*. J Hepatol 2020.

Key Points : HE (Disease state)

- HE is a major, life-limiting complication of advanced liver disease.
- Hyperammonemia due to impaired ammonia clearance is a major driver of HE.
- Standard-of-care therapeutics include lactulose and rifaximin.

Hepatic encephalopathy (HE)

GENFIT's program: VS-02-HE*

- *Vincent Forster, PhD, co-founder of VERSANTIS*

* investigational product that is not approved by any health authority

VS-02: novel oral investigational treatment for chronic hepatic encephalopathy

High unmet needs in hepatic encephalopathy (HE)

Growing prevalence driven by obesity, alcohol abuse, modern lifestyle

Goal: lower/stabilize ammonemia and prevent rehospitalization

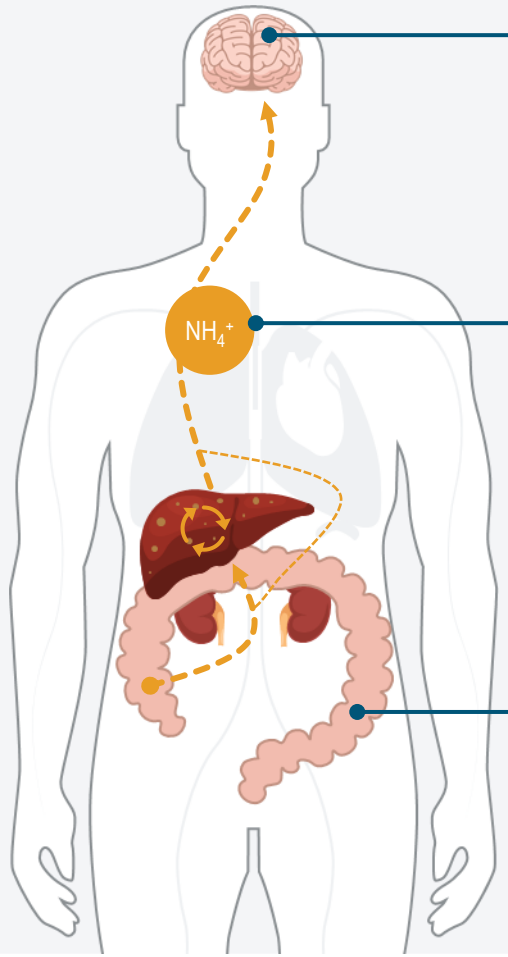
Oral route, acting locally in the colon

Novel urease inhibitor with IP protection up to 2042 (excluding any extension)

Promising preclinical data IND-enabling studies targeted completion in 2025

Hepatic encephalopathy (HE) is associated with elevated ammonia levels

Gut-Liver-Brain axis



Hepatic encephalopathy

- Glutamine accumulation
- Osmotic stress
- Alteration of cell metabolism

Hyperammonemia

- Inflammation
- Oxidative stress
- Bile acids ↑

Sources of ammonia

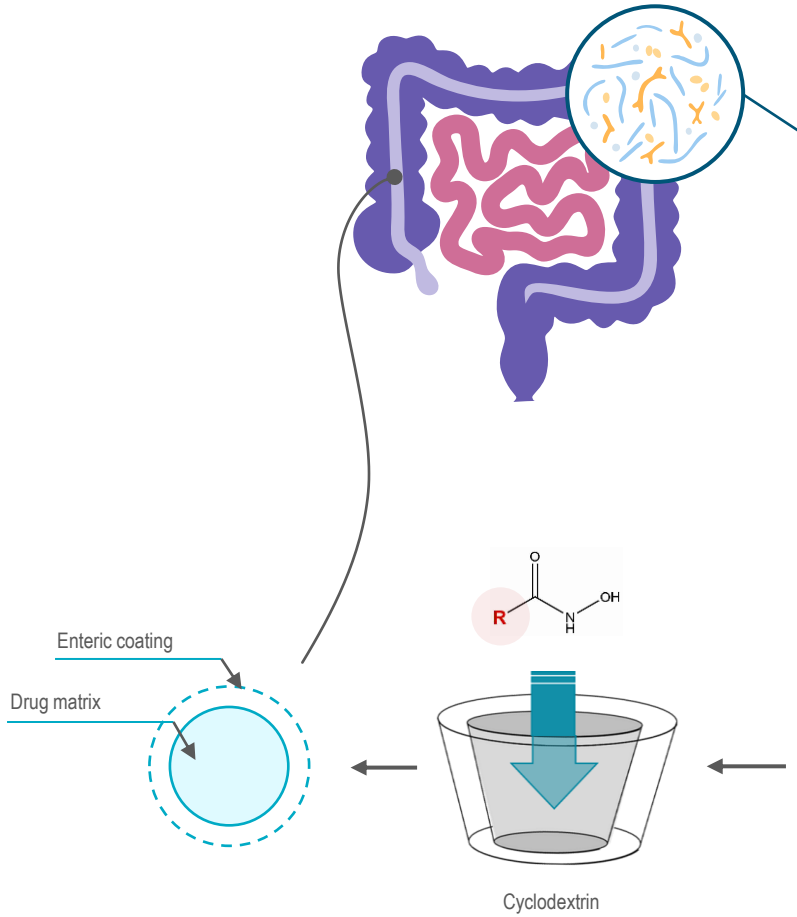
- Proteins degradation
- Urea hydrolysis

HE in brief

- Major & serious complication of liver cirrhosis affecting 30-45% of patients [1,2]
- In U.S.
  - 2M patients at risk to develop Overt HE; 200k patients hospitalized yearly [3]
  - Estimated annual economic burden of HE: $7.2 [4] in 2009 - $11.9+ billion in 2014 [4]
- Associated with increased hospitalizations, recurrences, healthcare costs and mortality
- Largely underdiagnosed and undertreated → poor quality of life
- Current treatments associated with side effects and moderate efficacy.
  Their goal: lowering ammonia levels

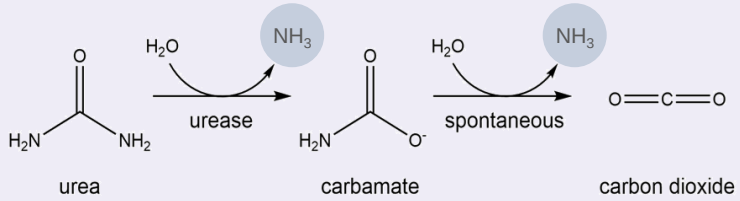
[1] Vilstrup *et al.*, Hepatology 2014 | [2] Poordad *et al.*, Aliment Pharmacol Ther 2007 | [3] Potnis *et al.*, International Journal of Hepatology 2021 | [4] Stepanova *et al.*, Clin Gast Hep 2012 | [5] Hirode *et al.*, Dig Dis Sci 2019

Urease inhibitors as treatment for HE



Urea hydrolysis by urease-producing bacteria

- Urea is secreted and actively transported into the intestine
- Gut bacteria produce urease to hydrolyze urea into ammonia
- 30% of all urea produced is hydrolyzed by gut microbiota, making it one of the main sources of ammonia [1]



Hydroxamic acids (HAs)

- Inhibit ureases by binding to nickel atoms in their active site [2]
- Hydroxamic acids today:
  - AcetoHA (Lithostat®) used for chronic urea-splitting urinary infection [3,4].
  - OctanoHA tested in patients with liver disease [5]
  - × Lack of potency
  - × Insufficient concentration in the colon
- 2-octynoHA is +10-fold more potent (IC50 = 0.038 mM) and can be delivered to the colon via colonic formulation as novel treatment for HE

VS-02

2-octynohydroxamic acid (2-octynoHA)

[1] Kappaun *et al.*, J Adv Res 2018 | [2] Kobashi *et al.*, Biochim Biophys Acta BBA - Enzymol 1971 | [3] Kashimura *et al.*, Kanzo 1974 | [4] Muri *et al.*, Hydroxamic acids, S. P. Gupta 2013 | [5] Summerskill *et al.*, Gastroenterology 1968

VS-02* has the potential to offer positive upsides vs standard of care

Drug	Technology	Indication	Limitations
Lactulose Various brands (global)	Laxative Route: oral MoA: reduce ammonia via bowel movements	Chronic HE Supportive for acute HE	- Poor compliance due to significant side effects (diarrhea & GI issues)
Rifaximin Xifaxan® (US, EU) Rifxima® (JP) BAUSCH Health NORGINE	Antibiotic Route: oral MoA: reduce ammonia via removal of gut bacteria	Recurrent HE	- Significant side effects and GI issues - Restricted to severe patients - Questionable safety of chronic antibiotherapy. Not for long-term use.
LOLA [1] Hepa-Merz® (EU) MERZ	Ammonia scavenger Route: oral and *i.v.* MoA: reduce ammonia via urea cycle support	Chronic & acute HE	- Not approved in the US - Effectiveness remains to be demonstrated and currently not recommended by guidelines [2]

VS-02 treatment goals

- Reduce hyperammonemia & stabilize blood ammonia at physiological level
- Prevent recurrence of overt HE and rehospitalizations
- Replace current standard of care associated with poor patient compliance due to side effects
- Increase access to care. HE remains largely underdiagnosed and undertreated [3]

*VS-02 is an investigational drug that is not approved by any Health Authority

Conclusions and forthcoming milestones

PROOF OF CONCEPT TO DATE

- VS-02 demonstrated superior urease inhibitory activity *in vitro* over +15 screened hydroxamic acid derivatives
- Synthesis of lead candidate optimized and straightforward
- *In vitro* and *in vivo* data planned **to be presented at EASL** and incorporated into a **peer-review publication** in H1:2023:
  - Cytotoxicity and mutagenicity assessment
  - *In vivo* efficacy to significantly reduce plasmatic ammonia and brain glutamine in bile duct-ligated rats
  - Preliminary *in vivo* pharmacokinetic assessment in dogs

FORTHCOMING MILESTONES

- Formulation optimization: colonic delivery capsules, stability assessment
- Manufacturing scale up
- IND-enabling nonclinical studies targeted for completion in 2025

Hepatic encephalopathy (HE)

Market opportunity

- *Pascal Caisey, Chief Operating Officer and Chief Commercial Officer of GENFIT*

Estimated[1] market opportunity in Hepatic Encephalopathy

Market opportunity

- Hepatic encephalopathy is a serious and potentially fatal complication of both acute and chronic liver failure
- It affects 30 to 40% of cirrhotic patients
- HE is probably one of the most frequent complication of cirrhosis that leads to hospitalizations and repeated re-admissions
- US
  - 2M patients at risk to develop HE
  - 200k hospitalized yearly.
  - Annual economic burden of HE hospitalizations: >$12bn
- EU
  - Incidence of HE close to 1M

- Market estimates[2]
  - Global market of $4.1bn by 2026

1: DelveInsight's "Hepatic Encephalopathy - Market Insights, Epidemiology, and Market Forecast-2030

2: Hepatic Encephalopathy Market Report by Coherent Market Insights

Short Q&A (5 minutes)

Questions?

GENFIT
TOWARDS BETTER MEDICINE

Cholangiocarcinoma (CCA)

Disease state

- *Dr Angela Lamarca, Medical Oncologist, Fundacion Jimenez Diaz University Hospital, Madrid, Spain*

Cholangiocarinoma

State of the Art and Unmet needs

19th October 2022

Dr Angela Lamarca MD, PhD, MSc

FEA / Honorary Consultant Medical Oncologist
Honorary Senior Lecturer

Department of Medical Oncology, Oncohealth Institute, Fundación Jimenez Diaz University Hospital, Madrid, Spain
Department of Medical Oncology, The Christie NHS Foundation Trust, Manchester, United Kingdom
University of Manchester, Manchester, United Kingdom

Disclosures

- Receipt of honoraria or consultation fees: EISAI, Nutricia Ipsen, QED, Roche, Servier, Boston Scientific, Albireo Pharma, AstraZeneca, Boehringer Ingelheim, GenFit and TransThera Biosciences.

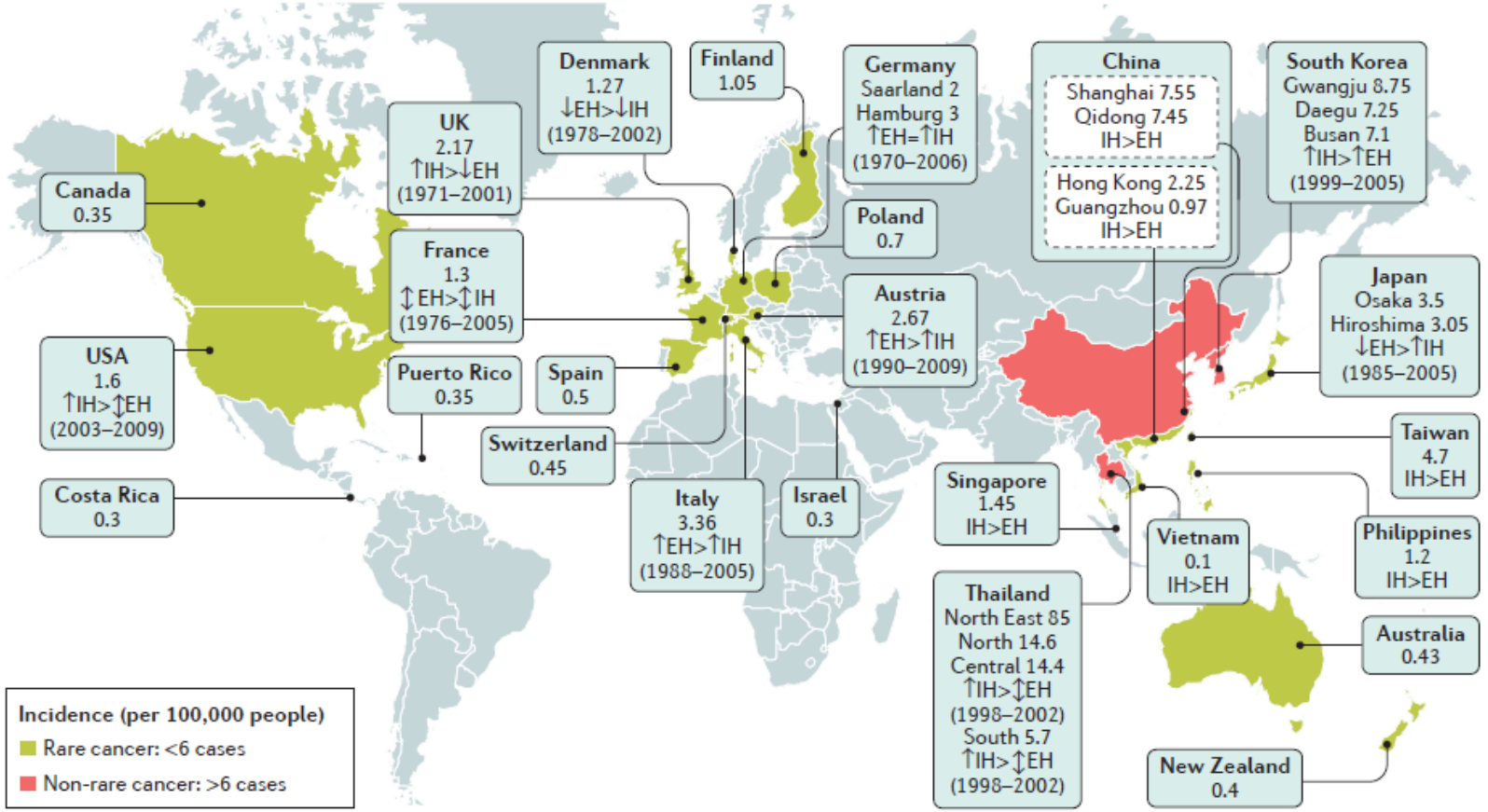
- Participation in company sponsored speaker bureau: Merck, Pfizer, Ipsen, Incyte, AAA, QED, Servier, Astra Zeneca, EISAI and Roche.

- Travel, education funding: Ipsen, Pfizer, Bayer, AAA, Sirtex, Delcath, Novartis, Mylan

- Research funding from Ipsen and Roche

Cholangiocarcinoma: Epidemiology

- Rare cancers
  - Incidence: <6/100,000
- Incidence increasing
  - iCCA
- Poor prognosis
  - 5-year OS (<20%)
  - Late diagnosis
    - 70% advanced stage
  - High relapse rate

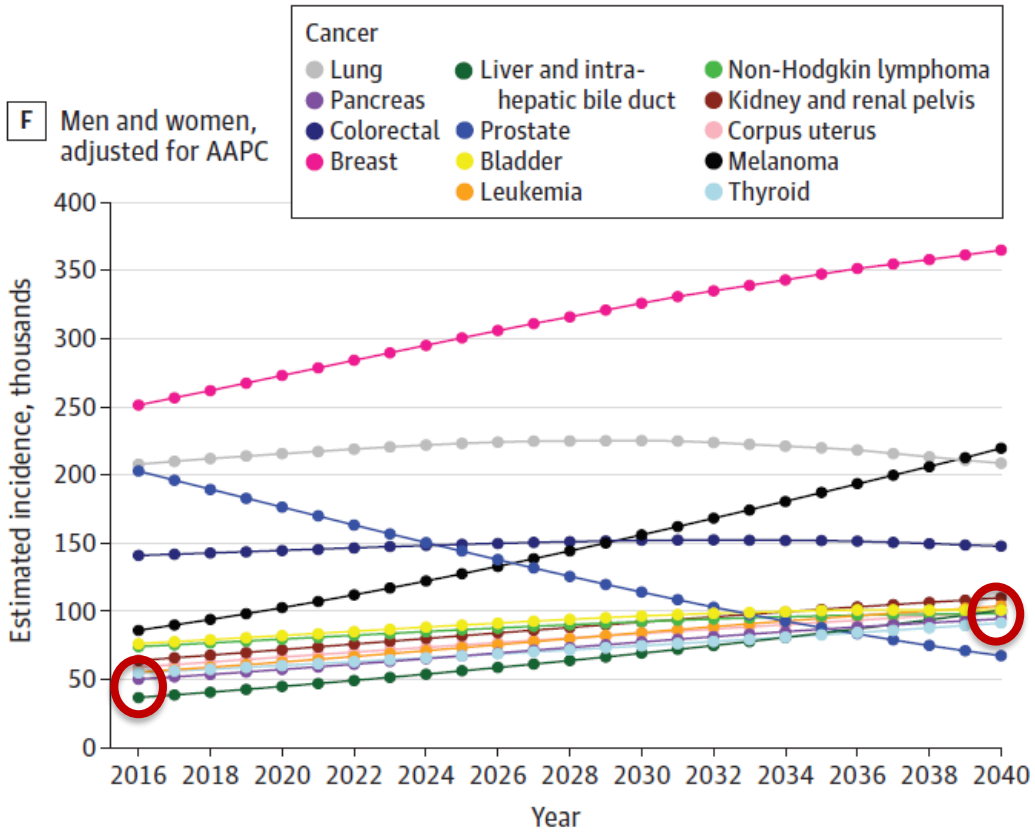


CCA, cholangiocarcinoma; EH, extrahepatic; iCCA, intrahepatic cholangiocarcinoma; IH, intrahepatic; OS, overall survival.

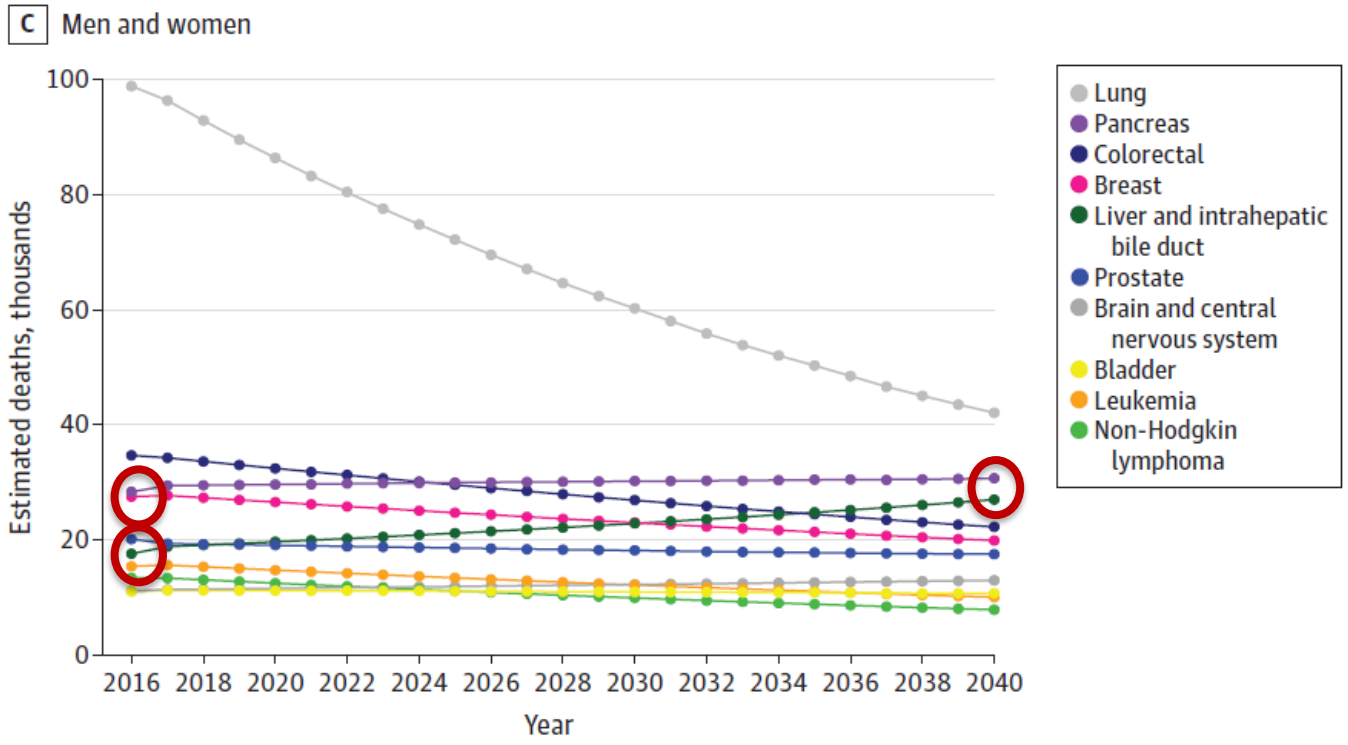
Bañales JM, et al. *Nat Rev Gastroenterol Hepatol*. 2016;13:261–80; DeOliveira ML, et al. *Ann Surg*. 2007;245:755–62; Valle JW, et al. *Ann Oncol*. 2016;27(Suppl 5):v28–37.

Cholangiocarcinoma: Incidence/mortality increasing

Estimated **incidence** projections (2016 → 2040)



Estimated **cancer death** projections (2016 → 2040)

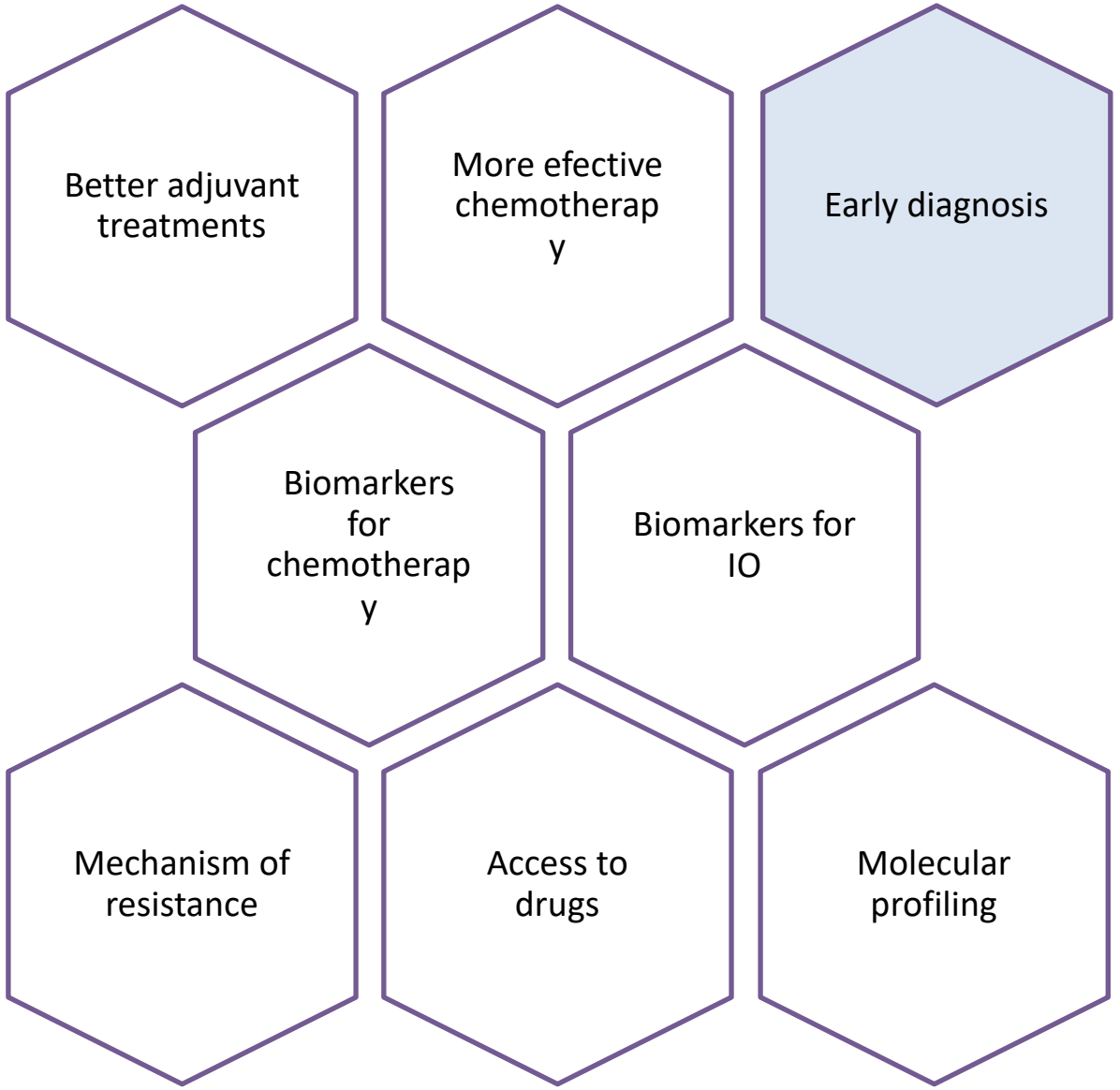


HPB cancers will be the second and third most common causes of cancer death by 2040

AAPC, average annual percent change; CCA, cholangiocarcinoma; HPB, hepato pancreatic biliary.

Rahib L, et al. *JAMA Netw Open*. 2021;4:e214708.

Unmet needs in Cholangiocarinoma



CCA - Heterogeneous

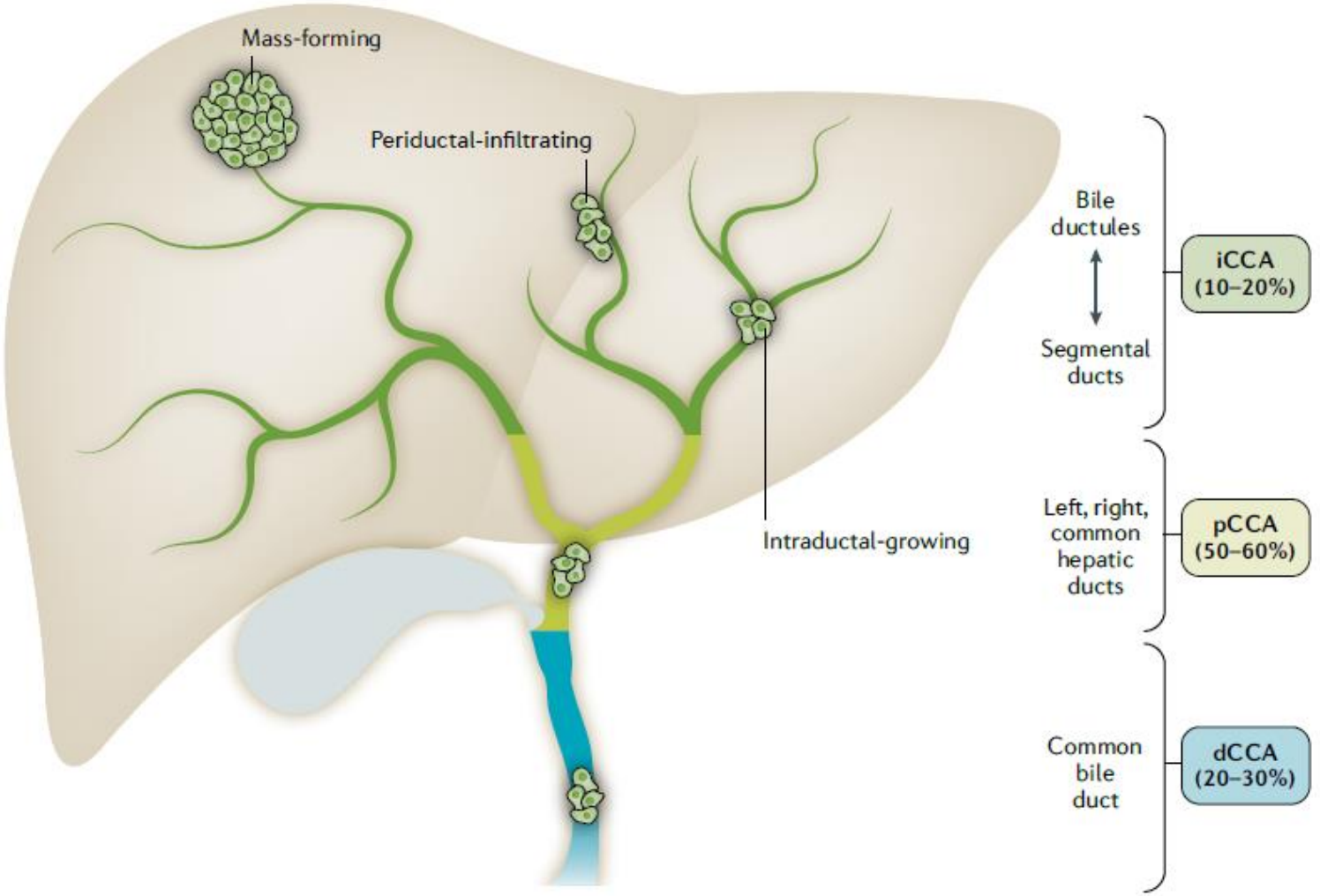
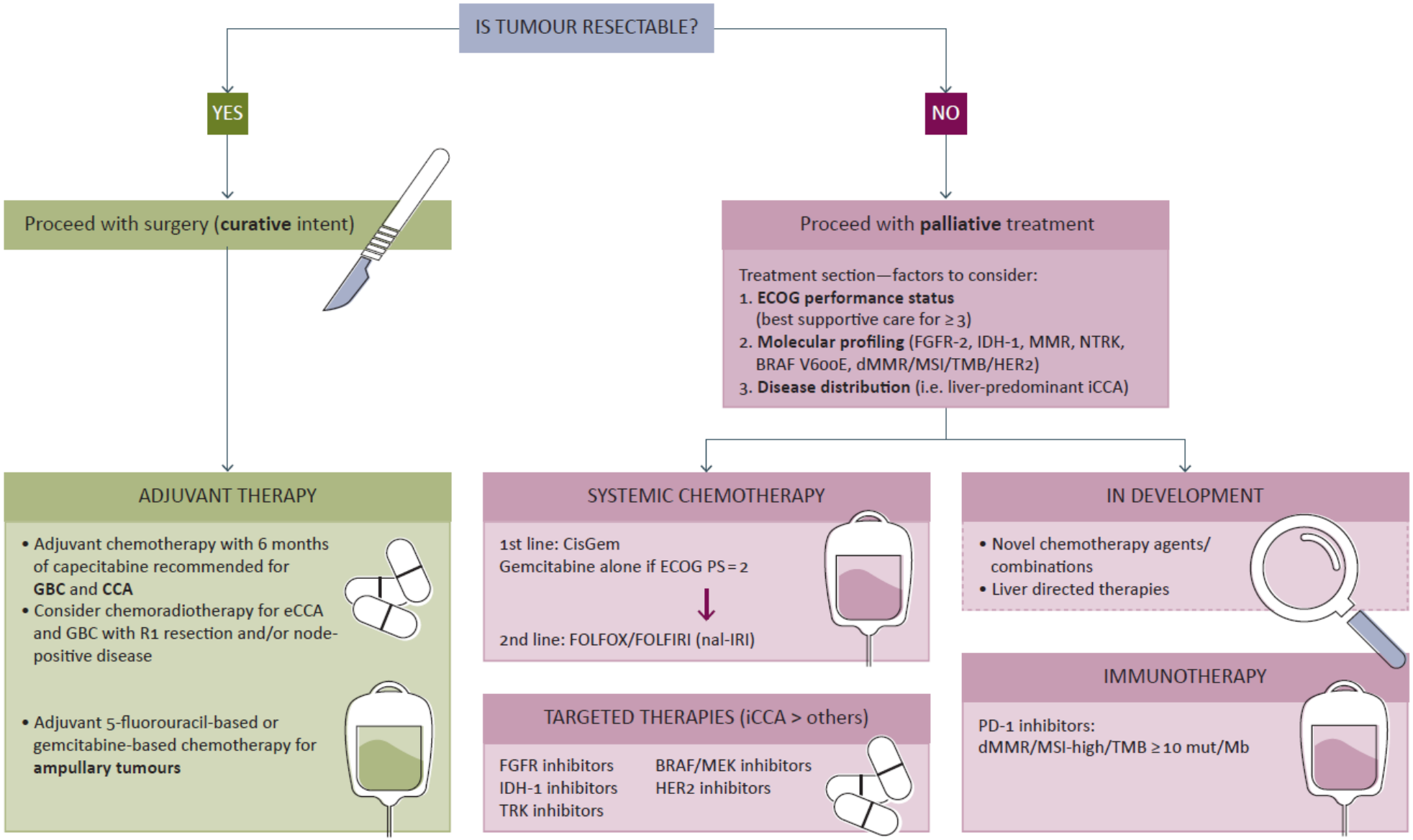


Fig. 1 | **Anatomical classification of cholangiocarcinoma.** On the basis of the anatomical site of origin,

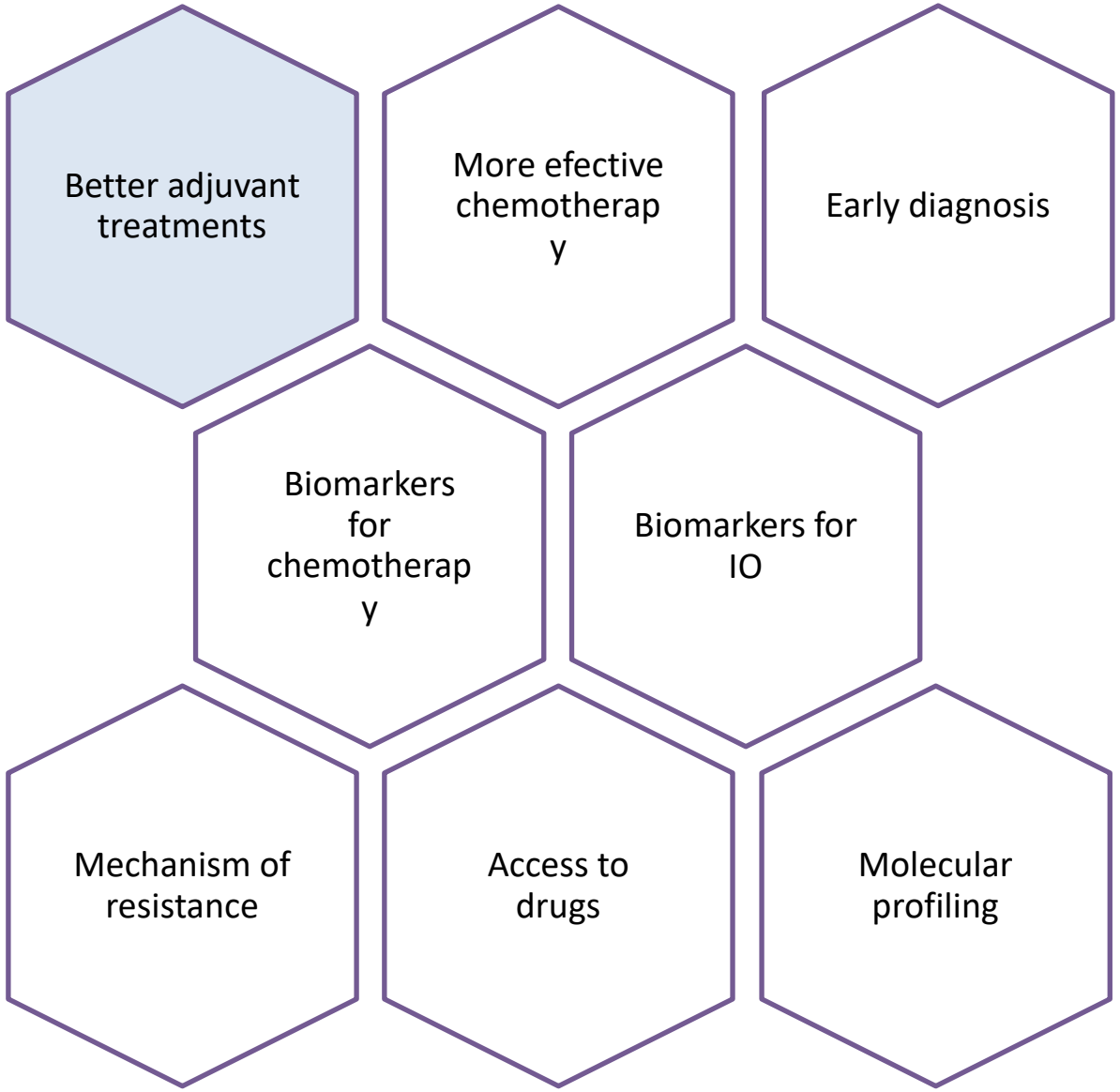
Bañales Nat Rev G&H 2020

Cholangiocarcinoma – Management Overview



Lamarca ESMO Open 2022

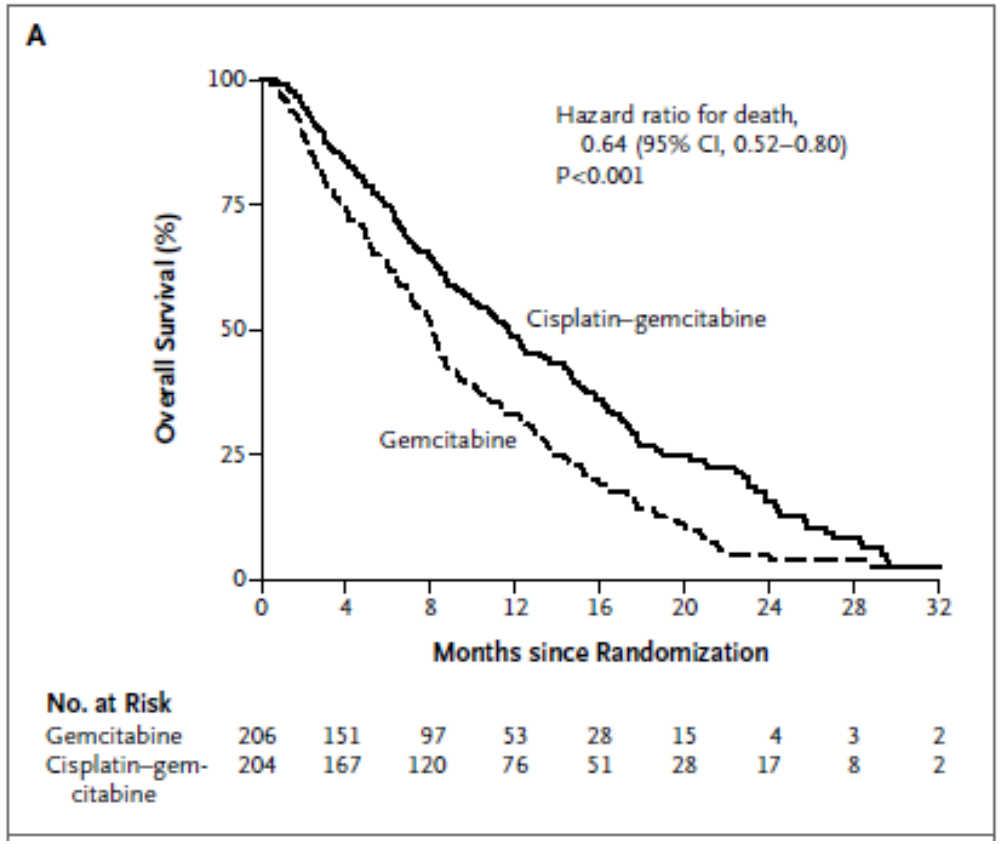
Unmet needs in CCA



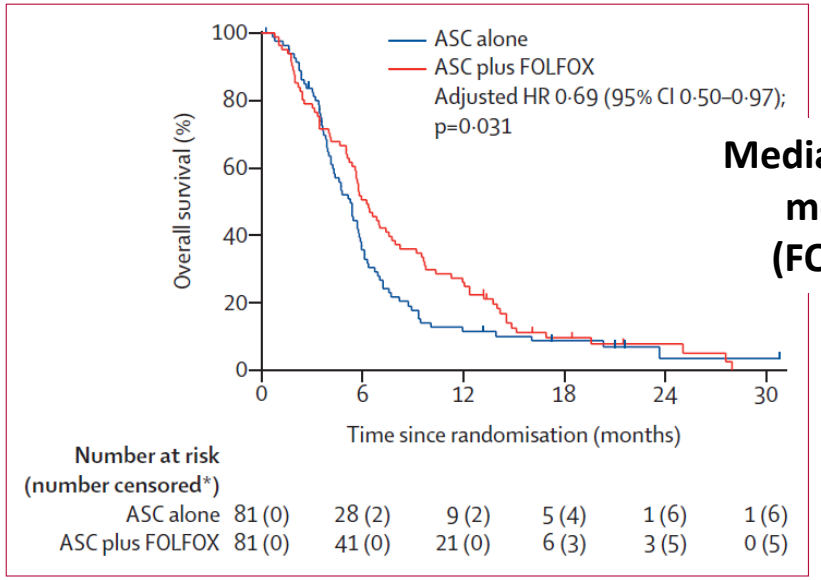
1L and 2L overview

1st Line Cis-Gem

Median OS 11.7 months (CisGem)

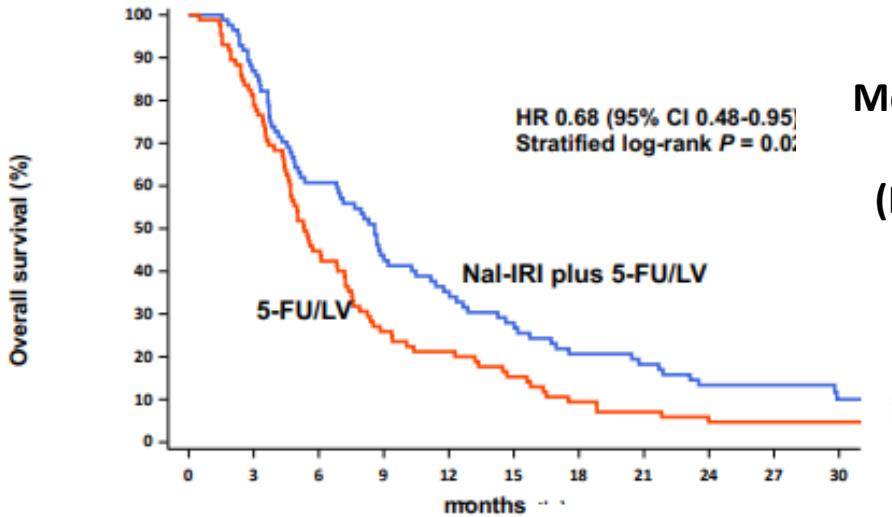


2nd Line FOLFOX / NlaIRI-5FU



Median OS 6.2 months (FOLFOX)

C.



Median OS 8.6 months (NalIRI-5FU)

Valle NEJM 2010; Lamarca Lancet Oncol 2021; Yoo ESMO 2022

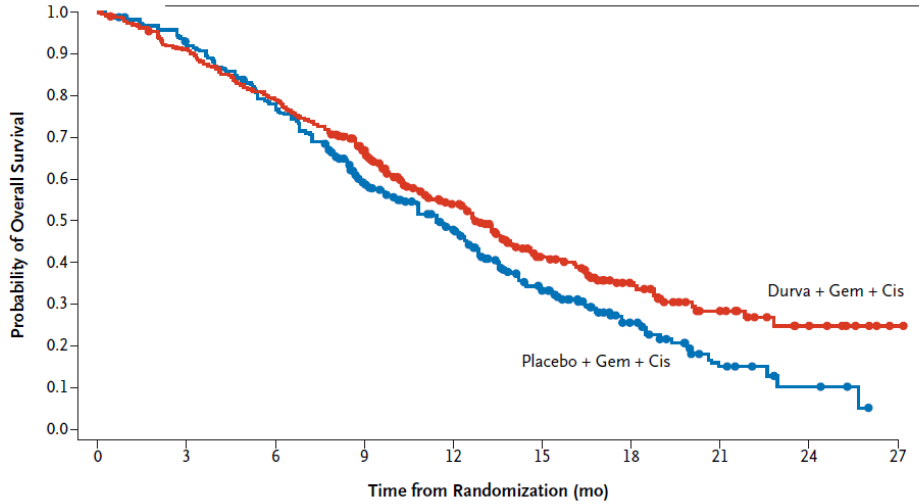
First-line – Durvalumab + CisGem (TOPAZ-1)

- TOPAZ-1: improved ORR/PFS/OS in favour of **Durvalumab + CisGem**

Median OS 12.8 months (CisGem+Durva – TOPAZ-1)
Median PFS 7.2 months (CisGem+Durva – TOPAZ-1)
ORR 26.7% (CisGem+Durva – TOPAZ-1)

A

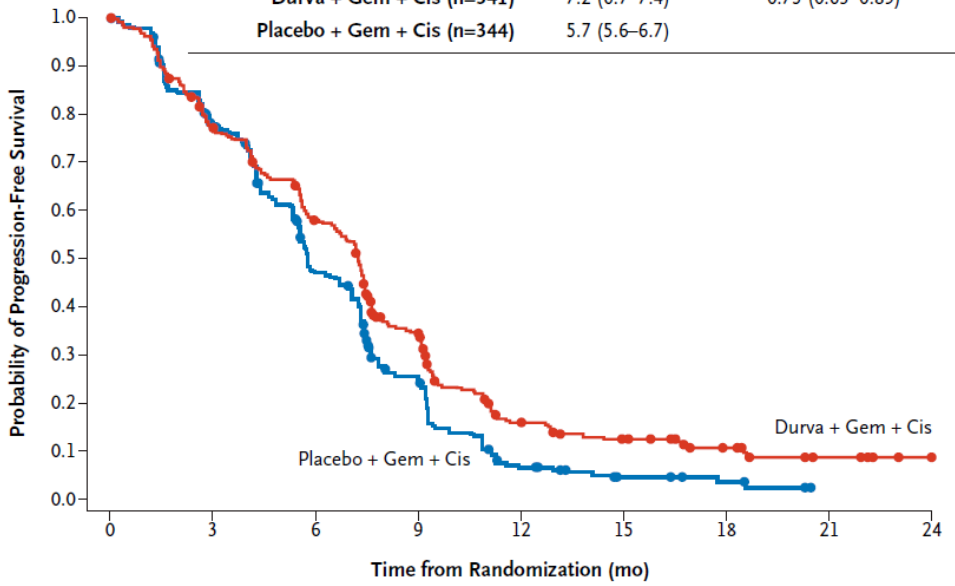
	Median Overall Survival, mo (95% CI)	Hazard Ratio (95% CI)	Stratified Log-rank P Value
Durva + Gem + Cis (n=341)	12.8 (11.1–14.0)	0.80 (0.66–0.97)	0.021
Placebo + Gem + Cis (n=344)	11.5 (10.1–12.5)		



No. at Risk

Durva + Gem + Cis	341	331	324	309	294	278	268	252	238	208	174	151	135	118	93	79	74	57	49	39	29	24	15	12	9	8	4	1
Placebo + Gem + Cis	344	337	329	317	299	283	261	242	220	183	159	143	125	97	78	65	52	40	29	21	15	10	8	4	4	3	0	0

	Median Progression-free Survival, mo (95% CI)	Hazard Ratio (95% CI)	Stratified Log-rank P Value
Durva + Gem + Cis (n=341)	7.2 (6.7–7.4)	0.75 (0.63–0.89)	0.001
Placebo + Gem + Cis (n=344)	5.7 (5.6–6.7)		



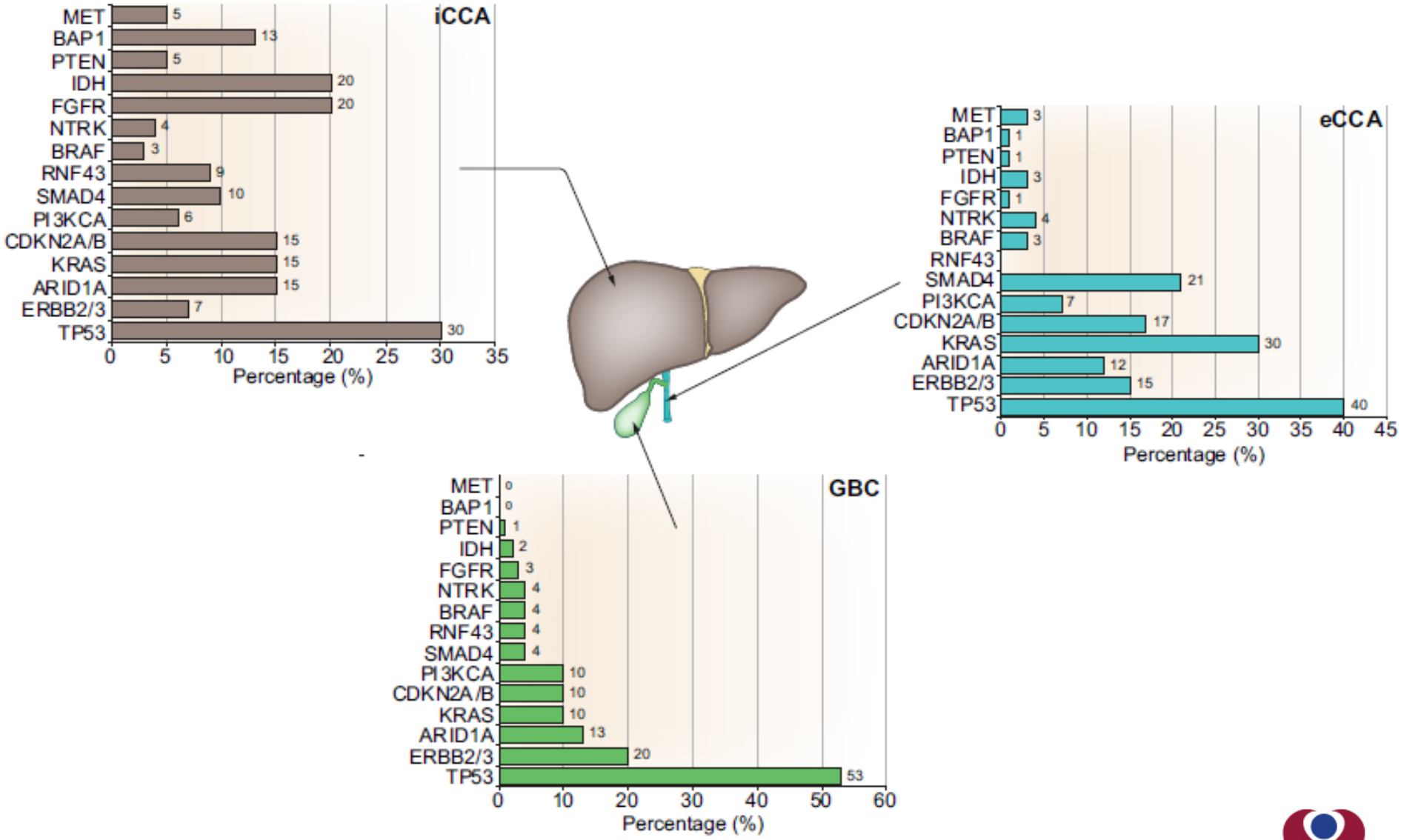
No. at Risk

Durva + Gem + Cis	341	326	296	258	245	221	189	174	106	100	62	54	38	31	27	25	23	16	15	7	7	5	4	1	0
Placebo + Gem + Cis	344	327	280	255	237	197	149	137	80	71	39	31	17	14	11	7	7	5	4	2	2	0	0	0	0

Oh NEJM Evidence 2022

Targeted therapies

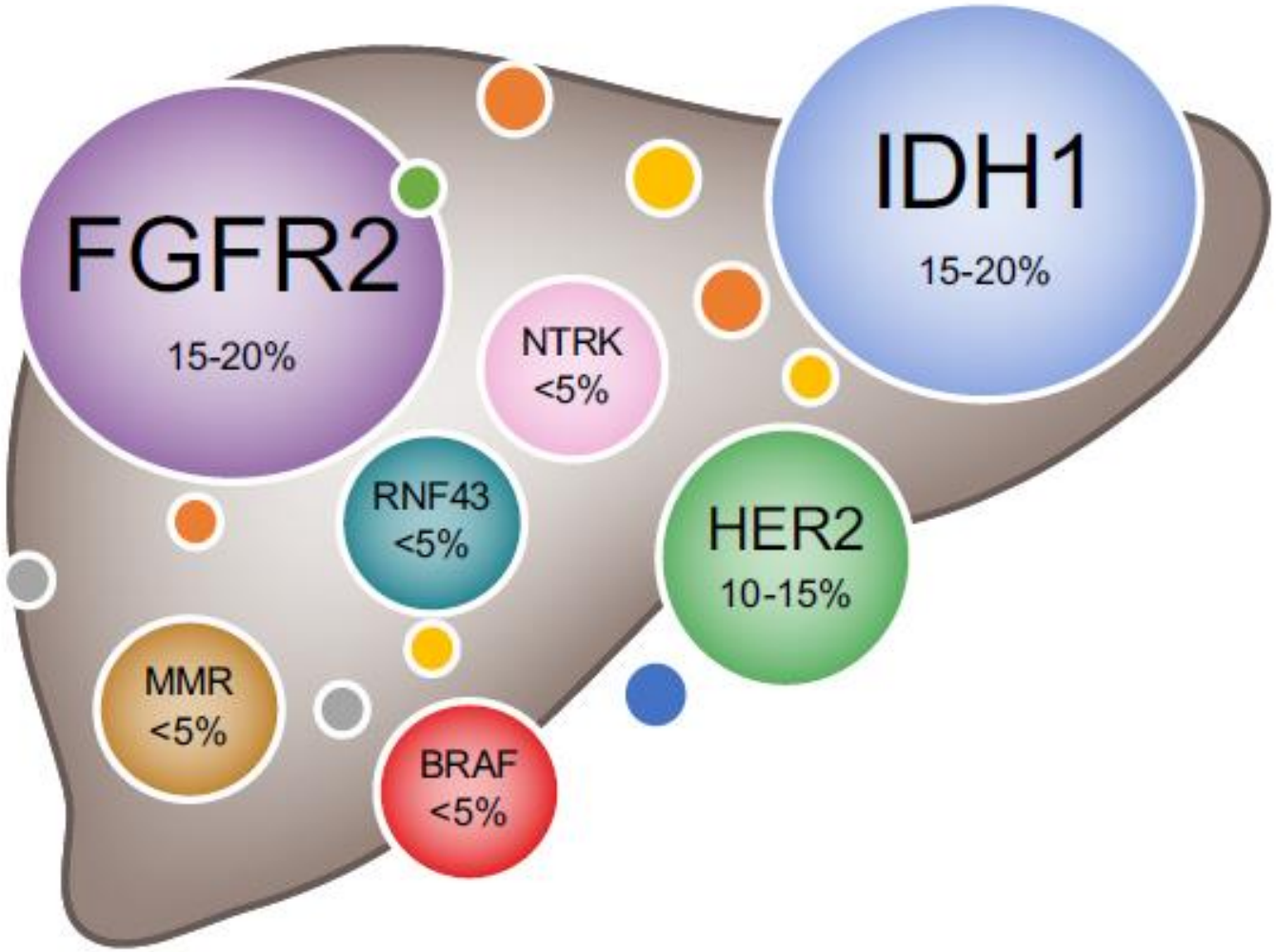
CCA: Precision medicine



Lamarca et al Journal of Hepatol 2020

CCA: Precision medicine

- BTC-specific
  - IDH-1 mutations
  - FGFR2 fusions
  - Other: BRAF, Her-2, KRAS
- Disease-agnostic
  - NTRK fusions
  - MMR-deficiency

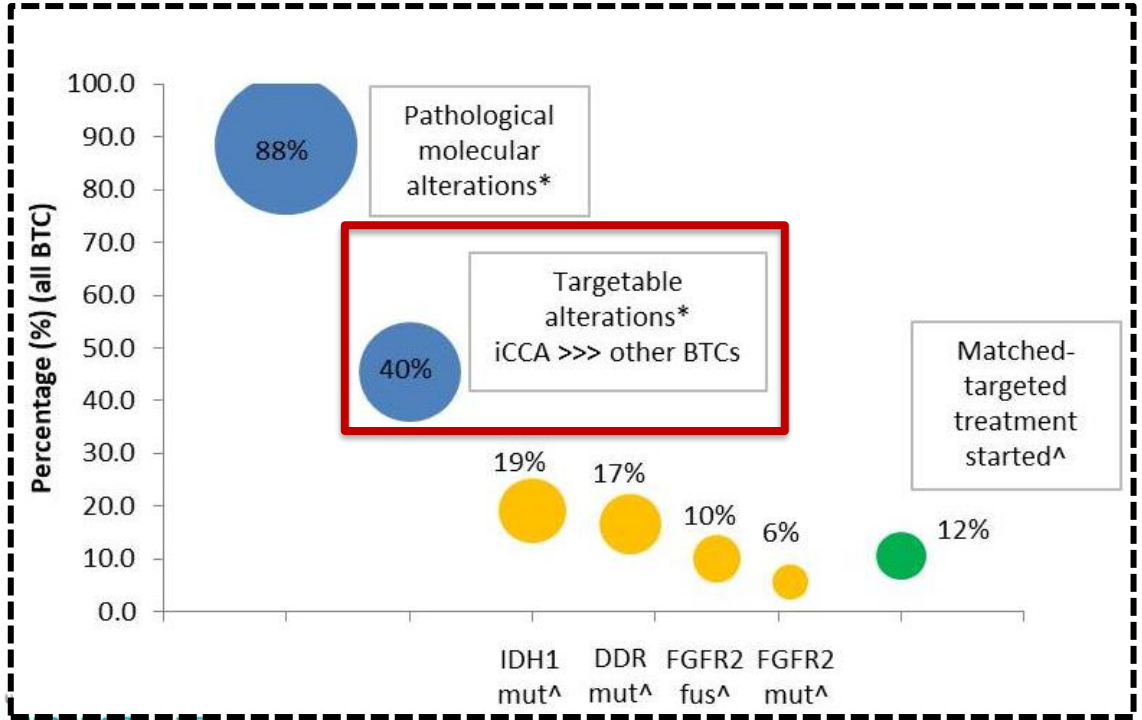


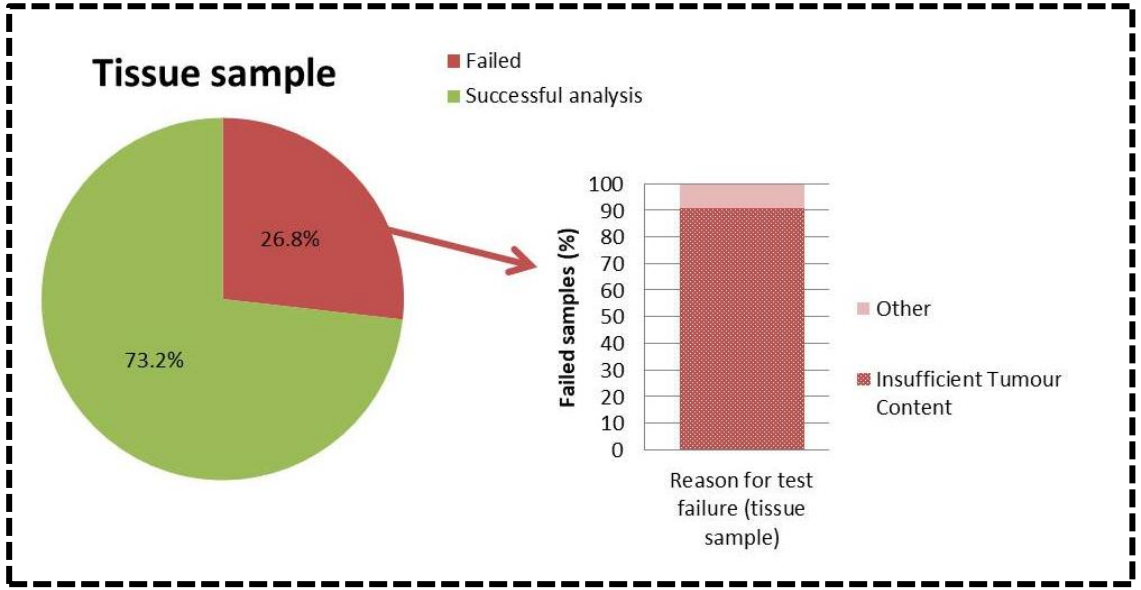
Lamarca et al Journal of Hepatol 2020

Challenges in delivering Precision Medicine in BTC

- Targetable findings in ~40% of patients
  - But to identify this:
    - Patient testing is crucial
    - Adequate tissue is needed
    - Early testing is needed to plan treatment options

- **Main challenge: quality tissue sample not always available**
  - Cytology-based diagnosis
  - Failed tissue samples

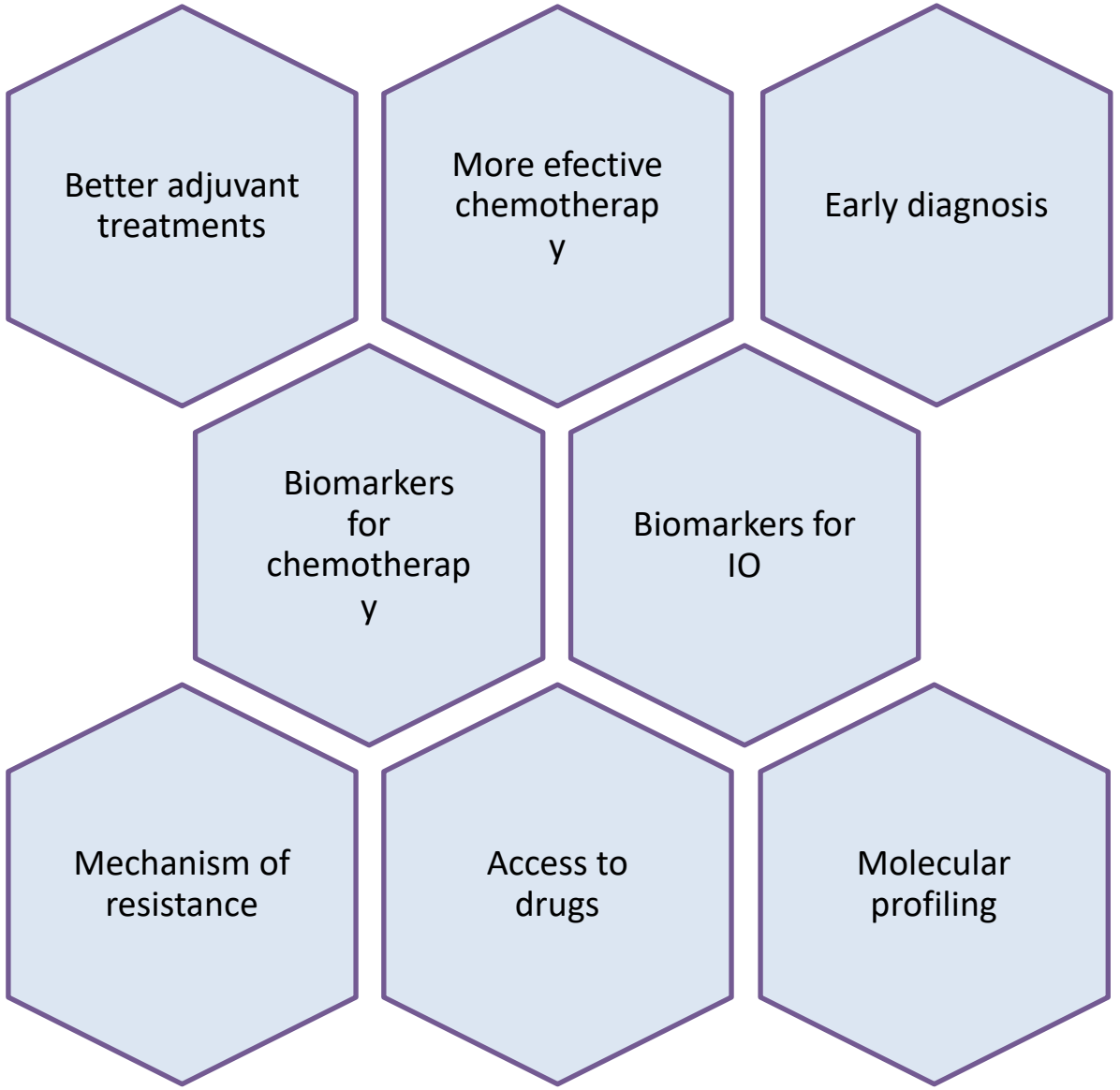




BTC, biliary tract cancer; CCA, cholangiocarcinoma; DDR, DNA damage repair; FGFR2, fibroblast growth factor receptor 2; iCCA, intrahepatic cholangiocarcinoma; IDH1, isocitrate dehydrogenase 1.

Lamarca A, et al. *J Clin Med*. 2020;9:2854.

Unmet needs in CCA



Summary Slide

- Unmet needs
- Opportunities
  - Novel mechanisms of action (e.g., autophagy inhibition)
  - Potential for combination/complementary MOAs
  - New targeted therapies (e.g., targeting KRAS)

Cholangiocarcinoma (CCA)

GENFIT's program: GNS561*

- *Dean Hum, PhD, Chief Scientific Officer of GENFIT*
- *Carol Addy, MD, Chief Medical Officer of GENFIT*

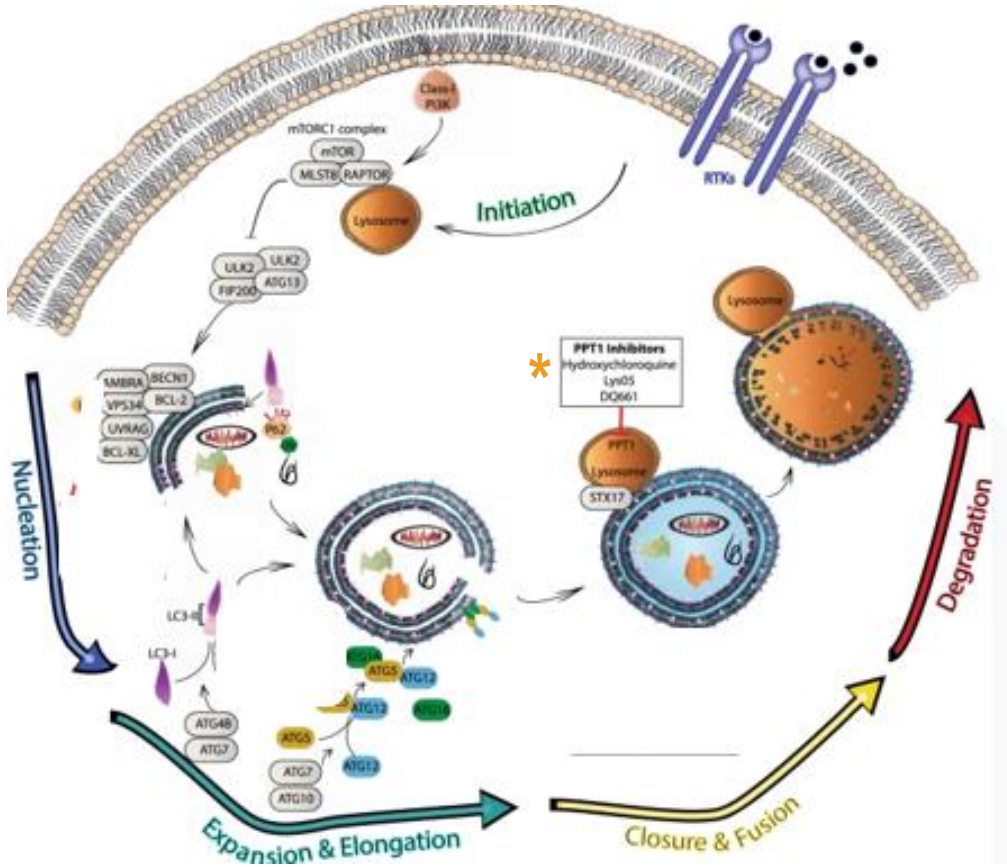
* investigational product that is not approved by any health authority

Autophagy and GNS561

Autophagy is a process that maintains cellular homeostasis and confers adaptation to environmental stresses, preventing cellular damage, and promoting cell survival.

In established tumors, autophagy facilitates development by promoting cancer cell proliferation and tumor growth.[1]

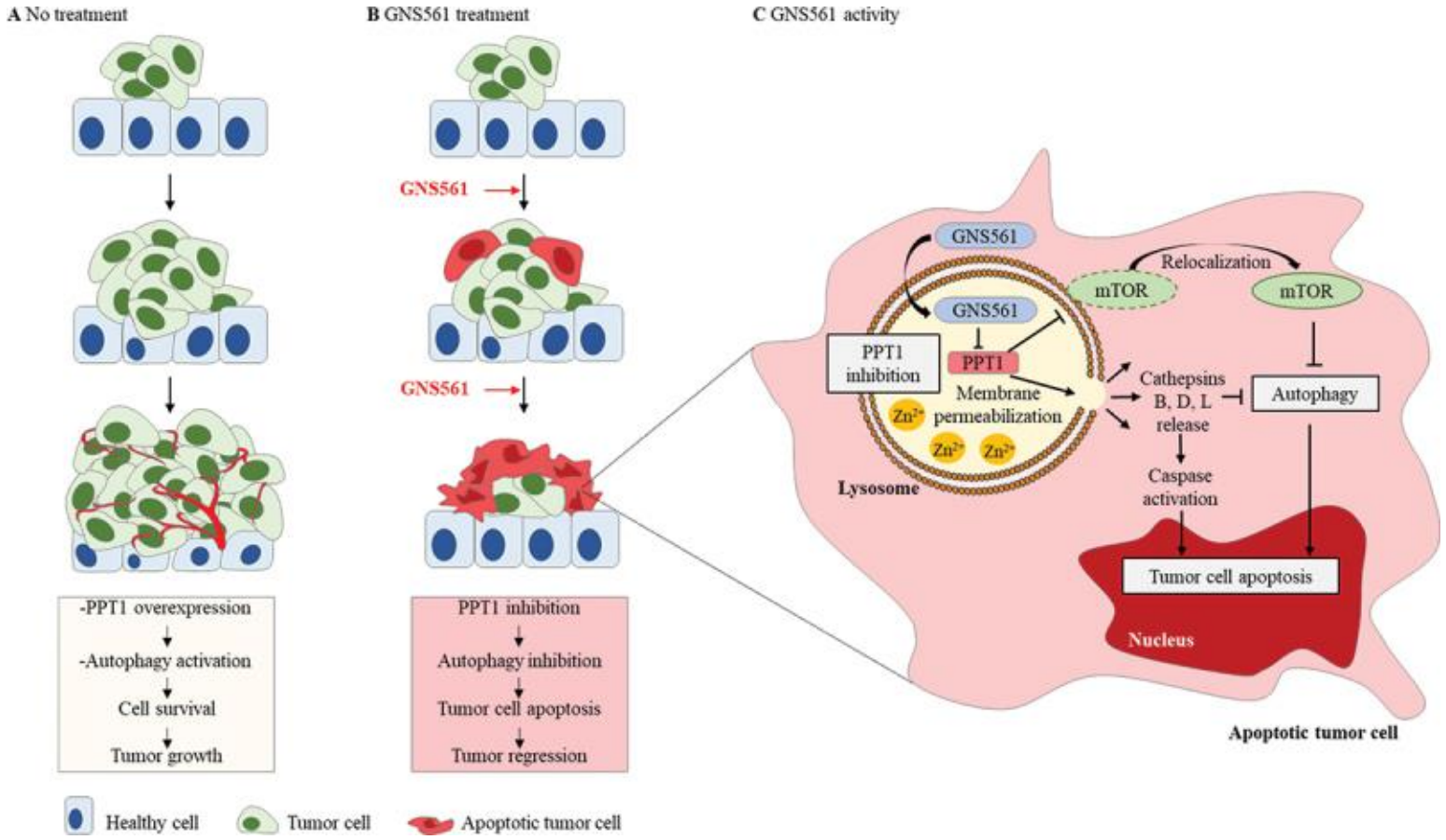
GNS561 is a **PPT1 inhibitor***, a small molecule that blocks cancer cell proliferation by inhibiting late-stage autophagy leading to cell death.[3]



Five stages of autophagy. *Adapted from Levy et al, 2020* [2]

1. Lim SM, Mohamad Hanif EA, Chin SF. Is targeting autophagy mechanism in cancer a good approach? The possible double-edge sword effect. Cell Biosci. 2021 Mar 20;11(1):56. doi: 10.1186/s13578-021-00570-z.
2. Mulcahy Levy JM, Thorburn A. Autophagy in cancer: moving from understanding mechanism to improving therapy responses in patients. Cell Death Differ. 2020 Mar;27(3):843-857. doi: 10.1038/s41418-019-0474-7.
3. Harding JJ, Awada A, Roth G, Decaens T, Merle P, Kotecki N, Dreyer C, Ansaldi C, Rachid M, Mezouar S, Menut A, Bestion EN, Paradis V, Halfon P, Abou-Alfa GK, Raymond E. First-In-Human Effects of PPT1 Inhibition Using the Oral Treatment with GNS561/Ezurpimtrostat in Patients with Primary and Secondary Liver Cancers. Liver Cancer. 2022 Feb 15;11(3):268-277. doi: 10.1159/000522418.

GNS561 Mechanism of Action



GNS561 localizes in lysosomes where it binds and **inhibits PPT1** resulting in:

- lysosomal unbound Zn2+ accumulation,
- impairment of cathepsin activity,
- autophagic flux inhibition,
- altered location of MTOR,
- lysosomal membrane permeabilization[1]

All these events induce caspase activation and **tumor cell apoptosis (cell death)**[1]

Genetic suppression of PPT1 impairs tumor growth and PPT1 levels are elevated in cancer and associated with poor survival[2]

Schematic representation of molecular and cellular mechanisms involved in the antitumoral activity of GNS561[1]

1. Brun S et al, GNS561, a clinical-stage PPT1 inhibitor, is efficient against hepatocellular carcinoma *via* modulation of lysosomal functions. Autophagy. 2022 Mar;18(3):678-694. doi: 10.1080/15548627.2021.
2. Rebecca VW et al. PPT1 Promotes Tumor Growth and Is the Molecular Target of Chloroquine Derivatives in Cancer. Cancer Discov. 2019 Feb;9(2):220-229. doi: 10.1158/2159-8290.CD-18-0706.

GNS561 has antitumor activity in human cancer cell lines and HCC* patient derived cells

Table 1. In vitro activity of GNS561 and HCQ in human cancer cell lines (left, IC_{50} ± SD, µM) and in vitro activity of GNS561 and sorafenib in primary HCC* patient-derived cells (right, IC_{50}, µM).

		Mean IC_{50} ± SD (µM)			IC_{50} (µM)	
Cancer type	Cell lines	GNS561	HCQ	Primary HCC patient-derived cells	GNS561	sorafenib
Colon Carcinoma	HCT-116	1.22 ± 0.15	14.41 ± 1.5	LI0050	3.54	9.12
	HT-29	1.35 ± 0.04	24.18 ± 5.14	LI0574	2.41	8.65
Renal Cell Carcinoma	786-O	1.72 ± 0.17	21.65 ± 3.15	LI0612	6.93	17.94
	CAKI-1	1.10 ± 0.19	17.69 ± 1.29	LI0752	0.49	6.34
Ovarian Cancer	NIH:OVCAR3	7.27 ± 1.71	98.01 ± 12.75	LI0801	2.07	5.7
Melanoma	A375	1.2 ± 0.13	12.27 ± 2.8	LI1005	3.16	14.49
	SK-MEL-28	1.81 ± 0.5	22.78 ± 2.65	LI1098	6.95	10.85
Breast Cancer	MDA-MB-231	2.17 ± 0.14	14.13 ± 3.06	LI1646	1.44	10.33
Prostate Cancer	DU-145	1.09 ± 0.18	45.74 ± 0.55	**Mean**	**3.37 ± 2.40**	**10.43 ± 4.09**
	PC-3	2.56 ± 0.23	43.43 ± 6.04			
Lung Cancer	A549	1.69 ± 0.34	14.33 ± 1.59			
	NCI-H358	2.54 ± 0.34	54.07 ± 14.19			
HCC	HepG2	0.47 ± 0.15	11.55 ± 1.52			
	Huh7	0.88 ± 0.31	13.62 ± 0.71			
Glioblastoma	LN-229	0.60 ± 0.24	10.87 ± 1.23			
	LN-18	0.22 ± 0.06	5.27 ± 0.74			
Acute Myeloid Leukemia	KG-1	5.86 ± 1.64	43.92 ± 2.76			
	Mean	**1.99 ± 1.86**	**27.52 ± 23.28**			

*HCC Hepatocellular Carcinoma

- GNS561 displays activity against human cancer cell lines and HCC patient-derived cells
- GNS561 was at least 10-fold more effective than HCQ in tested cancer cell lines
- GNS561 displayed activity in primary HCC patient-derived cells and was on average 3-fold more potent than sorafenib, a reference drug in HCC treatment

From Brun S et al. GNS561, a clinical-stage PPT1 inhibitor, is efficient against hepatocellular carcinoma *via* modulation of lysosomal functions. Autophagy. 2022 Mar;18(3):678-694. doi: 10.1080/15548627.2021.

GNS561 has antitumor activity in iCCA cell lines and iCCA patient-derived cells

Table 1 Mean $IC_{50} \pm SD$ of GNS561, gemcitabine and cisplatin in two human iCCA cell lines after 72 h of incubation

Cell lines	Mean $IC_{50} \pm SD$ (µM)		
	GNS561	Cisplatin	Gemcitabine
HuCCT1	1.5 ± 0.2	16.5 ± 0.5	75% max inhibition at 15 µM
RBE	1.7 ± 0.1	8.2 ± 1.2	60% max inhibition at 6 µM

Model name	GNS561		Gemcitabine		Cisplatin	
	IC_{50} (µM)	Maximal inhibition	IC_{50} (µM)	Maximal inhibition	IC_{50} (µM)	Maximal inhibition
CC6205	1.56	99.93%	0.026	86.3 7%	1.62	99.53%
CC6638	0.86	99.98%	> 10	49.16%	10.54	93.48%
CC6279	1.48	99.96%	0.010	83.73%	6.17	98.79%
CC6625	1.14	99.97%	13.61	52.57%	1.89	98.19%
CC6658	1.23	100.00%	0.53	89.98%	0.85	99.81%

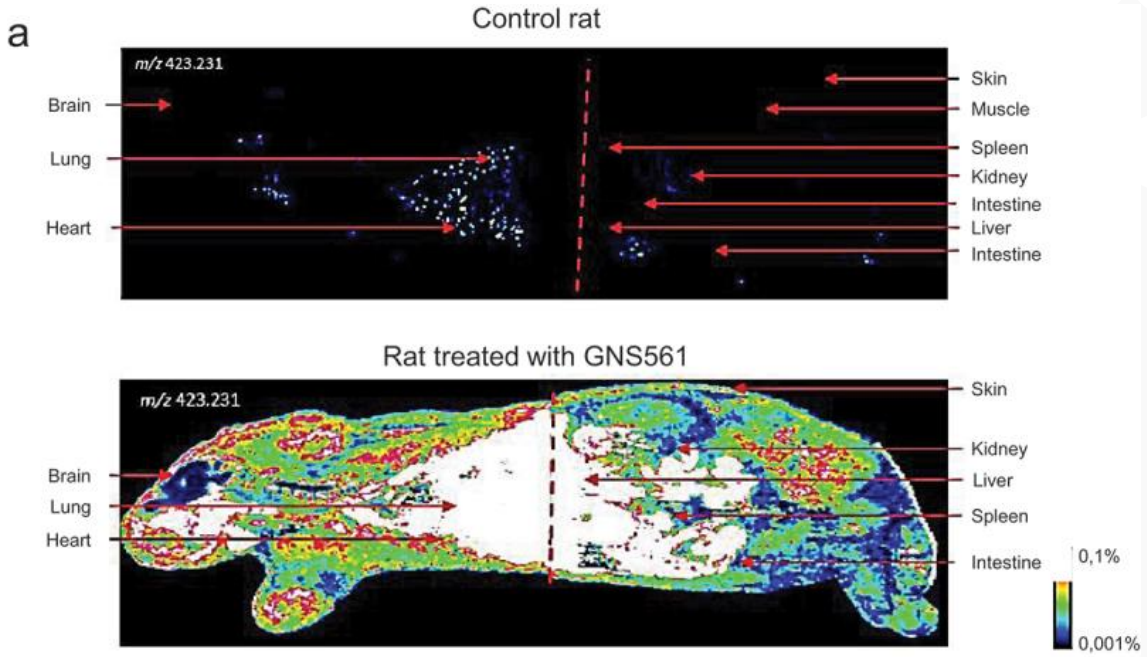
GNS561 significantly reduced cell viability in two iCCA cell lines (IC50 of 1.5 ± 0.2 µM in HuCCT1 and IC50 of 1.7 ± 0.1 µM in RBE cells (Table 1).

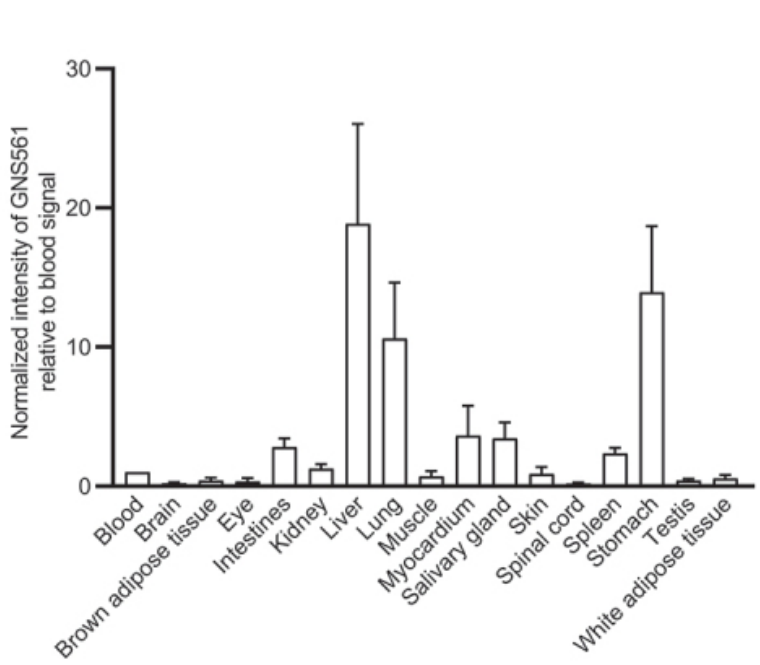
GNS561 was more potent than cisplatin or gemcitabine in 2 models (CC6638 and CC6279, and CC6638 and CC6625, respectively). GNS561 was as effective as cisplatin in 3 out 5 iCCA patient-derived cell line models (CC6205, CC6625 and CC6658).

GNS561 always induced a complete tumor inhibition in all models contrary to gemcitabine which did not in any model, suggesting that GNS561 may be efficient in models with low sensitivity to gemcitabine.

From Brun S, Bassissi F, Serdjebi C, Novello M, Tracz J, Autelitano F, Guillemot M, Fabre P, Courcambeck J, Ansaldi C, Raymond E, Halfon P. GNS561, a new lysosomotropic small molecule, for the treatment of intrahepatic cholangiocarcinoma. Invest New Drugs. 2019 Dec;37(6):1135-1145. doi: 10.1007/s10637-019-00741-3.

GNS561 mainly accumulated in the liver, stomach and lung

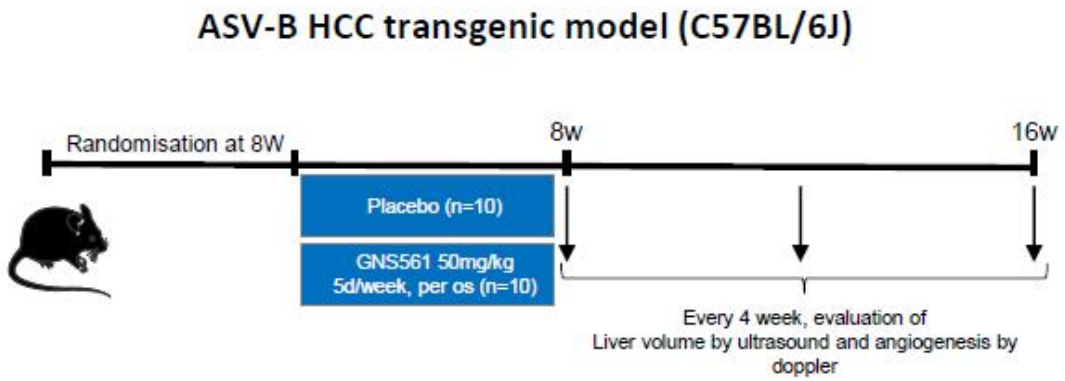


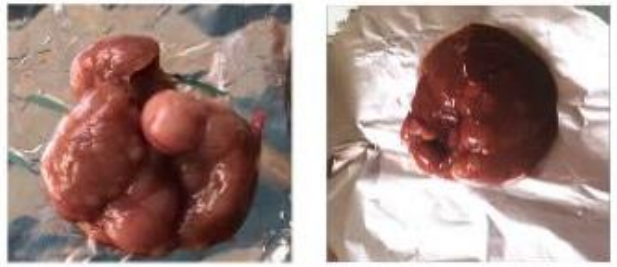


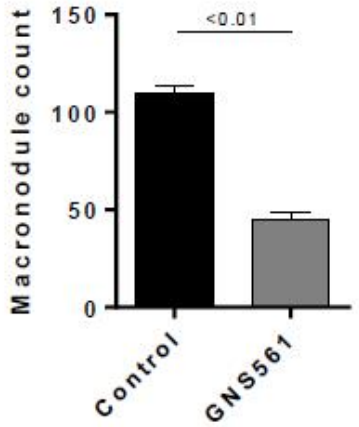
Whole body tissue distribution of GNS561.
Mass spectrometry imaging of a control rat (top) and a rat treated with GNS561 (bottom) at a dose of 40 mg/kg/day for 28 days.

From Brun S et al. GNS561, a new lysosomotropic small molecule, for the treatment of intrahepatic cholangiocarcinoma. Invest New Drugs. 2019 Dec;37(6):1135-1145. doi: 10.1007/s10637-019-00741-3.

GNS561 decreases tumor number and size in transgenic HCC mouse model





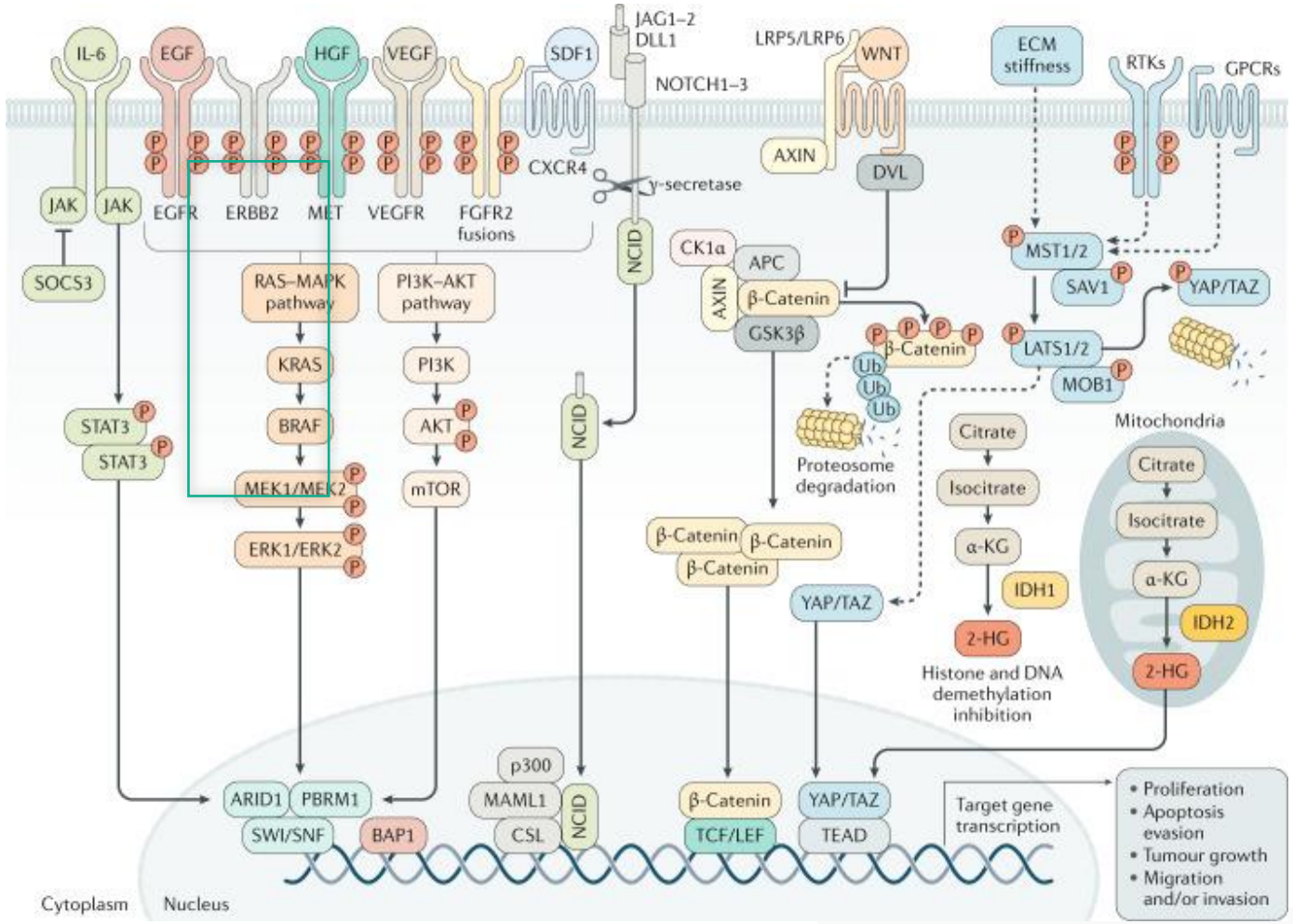


→ **GNS561 decreases tumor macronodule number**

Philippe Halfon[1], Madani Rachid[1], Cindy Serdjebi[1], Annemilaï Tijeras-Raballand[2] , Sonia Brun[1], Christelle Ansaldi[1], Eric Raymond[1,2], [1]Genoscience Pharma, Marseille, France, [2]AFR Oncology, Boulogne-Billancourt, France
GNS561, A NEW ORAL CLINICAL-STAGE SMALL MOLECULE COMBINED WITH A PD-1 INHIBITOR SHOWED REMARKABLE ANTI-TUMOR EFFECTS IN A TRANSGENIC IMMUNOCOMPETENT HEPATOCELLULAR CARCINOMA MOUSE MODEL (ASV-B), AASLD 1993

Therapeutical approach in CCA

Signalling pathways involved in CCA development and progression[1]



- CCA identified as RAS driven cancer with important role of MAPK pathway activation[1]
- Evidence for targeting autophagy, through the concomitant blocking of MAP kinase pathway (activated in KRAS CCA) to create synergistic inhibition in pancreatic cancer[2]
- Combination with MEK inhibitor and autophagy inhibitor relevant in KRAS mutated CCA population

1. Banales JM et al, Cholangiocarcinoma 2020: the next horizon in mechanisms and management. Nat Rev Gastroenterol Hepatol. 2020 Sep;17(9):557-588. doi: 10.1038/s41575-020-0310-z.
2. Kinsey CG et al. Protective autophagy elicited by RAF→MEK→ERK inhibition suggests a treatment strategy for RAS-driven cancers. Nat Med. 2019 Apr;25(4):620-627. doi: 10.1038/s41591-019-0367-9.

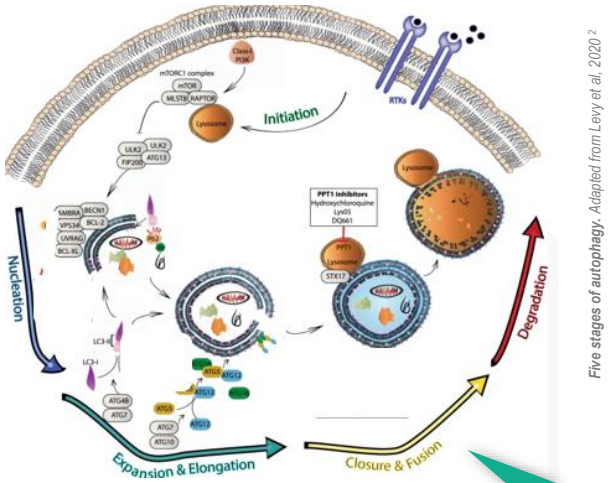
Combination of existing therapy with GNS561 (inhibition of autophagy) to synergistically decrease cancer cell survival and tumor growth

Anti-cancer Therapies
-Chemotherapeutic agents
-MAP Kinase pathway targeted therapies
-Immune checkpoint inhibitors (anti-PD-1/PD-L1)

Cancer cells Survival mechanisms

autophagy

Promotes cancer cell survival, tumor growth and resistance to treatment



Five stages of autophagy. Adapted from Levy et al, 2020 [2]

Beneficial anti-cancer effects

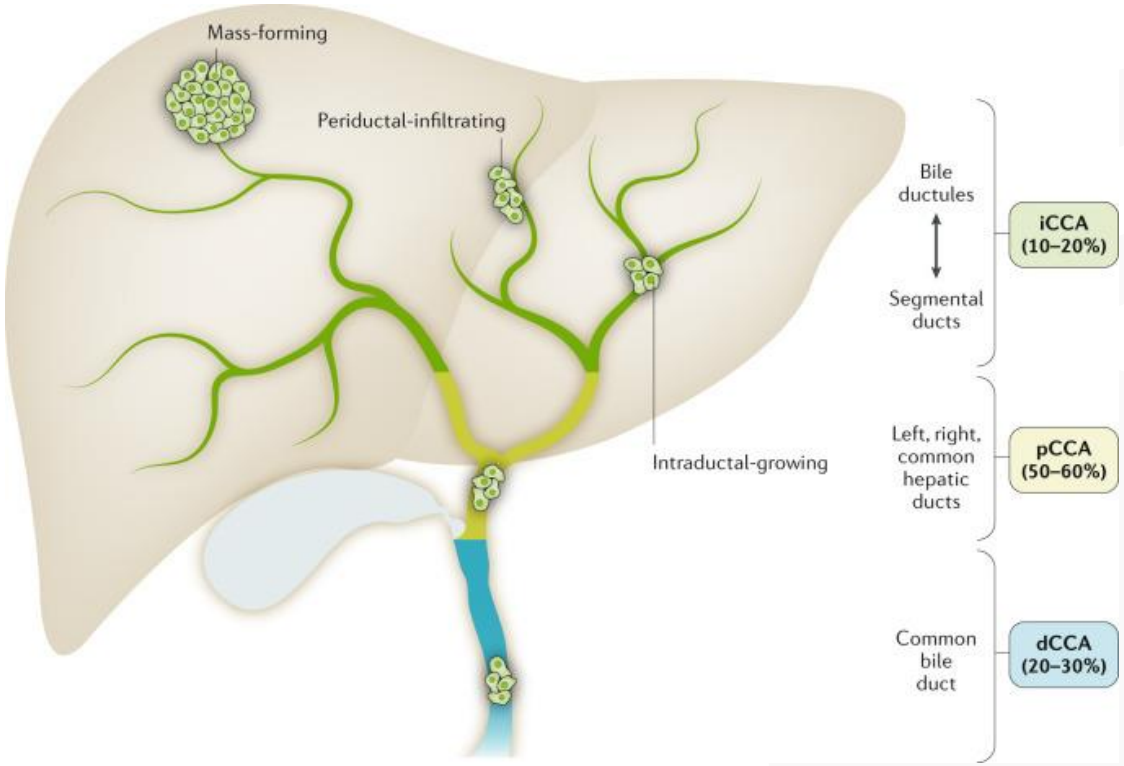
↓ cancer **cell survival**

↓ cancer **growth**

GNS561 (PPT1 inhibitor)

Blocks cancer cell survival
by inhibiting late-stage autophagy

Rate of KRAS mutation in CCA is frequent: estimated between 20% (iCCA) and 40% (eCCA)



20% of iCCA are estimated to have KRAS mutations[2,3]

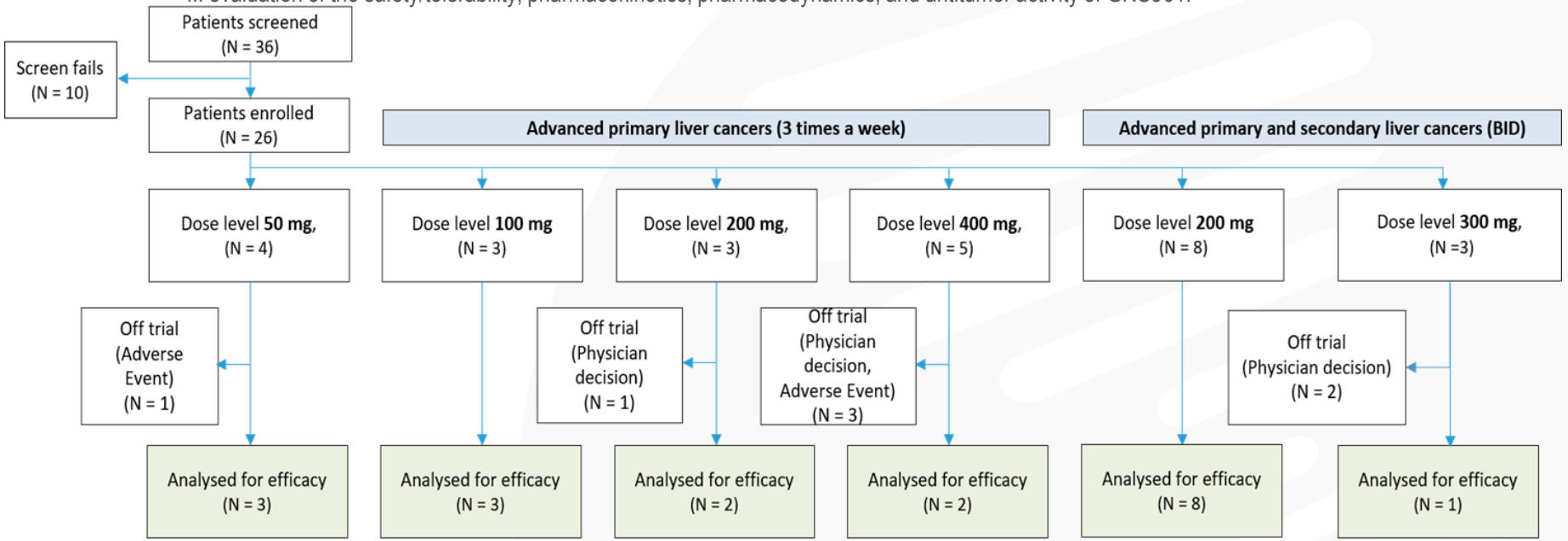
40% of eCCA are estimated to have KRAS mutations[2,3]

From Banales JM et al, Cholangiocarcinoma 2020: the next horizon in mechanisms and management. Nat Rev Gastroenterol Hepatol. 2020 Sep;17(9):557-588. doi: 10.1038/s41575-020-0310-z.
2. Comprehensive genomic profiling of biliary tract cancers to reveal tumor-specific differences and frequency of clinically relevant genomic alterations.
Jeffrey S. Ross, Kai Wang, Milind M. Javle, Daniel Virgil Thomas Catenacci, Rachna T. Shroff, Siraj Mahamed Ali, Julia Andrea Elvin, Juliann Chmielecki, Roman Yelensky, Doron Lipson, Vincent A. Miller, Philip J. Stephens, and Funda Meric-Bernstam Journal of Clinical Oncology 2015 33:15_suppl, 4009-4009
3. Pellino A, Loupakis F, Cadamuro M, Dadduzio V, Fassan M, Guido M, Cillo U, Indraccolo S, Fabris L. Precision medicine in cholangiocarcinoma. Transl Gastroenterol Hepatol. 2018 Jul 12;3:40. doi: 10.21037/tgh.2018.07.02.

First-In-Human Effects of PPT1 Inhibition Using the Oral Treatment GNS561 in Patients with Primary and Secondary Liver Cancers – Study design/Results

Flow diagram of the Phase I, open-label, dose-escalation trial (3 + 3 design)

Objectives I: to determine GNS561 recommended phase II dose (RP2D) and schedule.
II: evaluation of the safety/tolerability, pharmacokinetics, pharmacodynamics, and antitumor activity of GNS561.



- 3 times a week administration was associated with limited exposure and the BID schedule was preferred.
- At 200 mg BID GNS561, plasma and liver concentrations were comparable to active doses in animal models.

Source: Harding JJ, Awada A, Roth G, Decaens T, Merle P, Kotecki N, Dreyer C, Ansaldi C, Rachid M, Mezouar S, Menut A, Bestion EN, Paradis V, Halfon P, Abou-Alfa GK, Raymond E. First-In-Human Effects of PPT1 Inhibition Using the Oral Treatment with GNS561/Ezurpimtrostat in Patients with Primary and Secondary Liver Cancers. Liver Cancer. 2022 Feb 15;11(3):268-277. doi: 10.1159/000522418.

First-In-Human Effects of PPT1 Inhibition Using the Oral Treatment GNS561 in Patients with Primary and Secondary Liver Cancers – Results

Table 2. Safety of escalated doses of GNS561

Treatment-related AEs *n* (%)			
Grade	1–2	3	Total
Nausea	13 (50)	–	13 (50)
Vomiting	14 (54)	–	14 (54)
Diarrhea	9 (35)	2 (8)	11 (42)
Decreased appetite	2 (8)	1 (4)	3 (12)
Abdominal pain	2 (8)	–	2 (8)
Abdominal distension	2 (8)	–	2 (8)
Constipation	1 (4)	–	1 (4)
Fever	1 (4)	–	1 (4)
Dyspepsia	1 (4)	–	1 (4)
Regurgitation	1 (4)	–	1 (4)
Weight decreased	1 (4)	–	1 (4)
Fatigue	5 (19)	1 (4)	6 (23)
Dizziness	1 (4)	–	1 (4)
Occasional weakness	1 (4)	–	1 (4)
Asthenia	1 (4)	1 (4)	2 (8)
Sweating	1 (4)	–	1 (4)
Blood zinc decreased	2 (8)	–	2 (8)
Anemia	1 (4)	–	1 (4)
ALT increased	–	1 (4)	1 (4)
AST increased	1 (4)	1 (4)	2 (8)
Increased bilirubin level	2 (8)	–	2 (8)
Blood albumin decreased	1 (4)	–	1 (4)
Hypertension	1 (4)	–	1 (4)
Dyspnea	1 (4)	–	1 (4)
Blurred vision	1 (4)	–	1 (4)
Hypercalcemia	1 (4)	–	1 (4)
Nephritic pain	1 (4)	–	1 (4)
Dry mouth	1 (4)	–	1 (4)
Cough	1 (4)	–	1 (4)
Peripheral sensory neuropathy	1 (4)	–	1 (4)
Mucosal inflammation	1 (4)	–	1 (4)

26 evaluable patients for safety

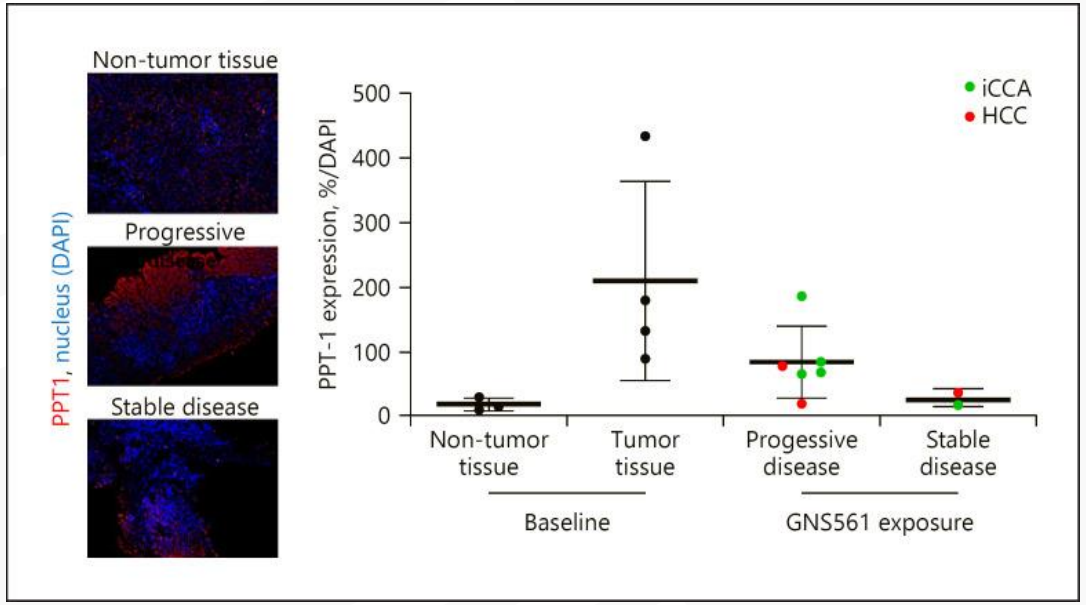
Adverse events (AEs) included gastrointestinal grade 1–2 events:
- Nausea in 13 (50%)
- Vomiting in 14 (54%)
- Diarrhea in 11 (42%) patients

7 grade 3 AEs reported

No dose-limiting toxicity observed

No treatment-related deaths occurred.

- Five patients experienced tumor stable diseases, including one minor response.



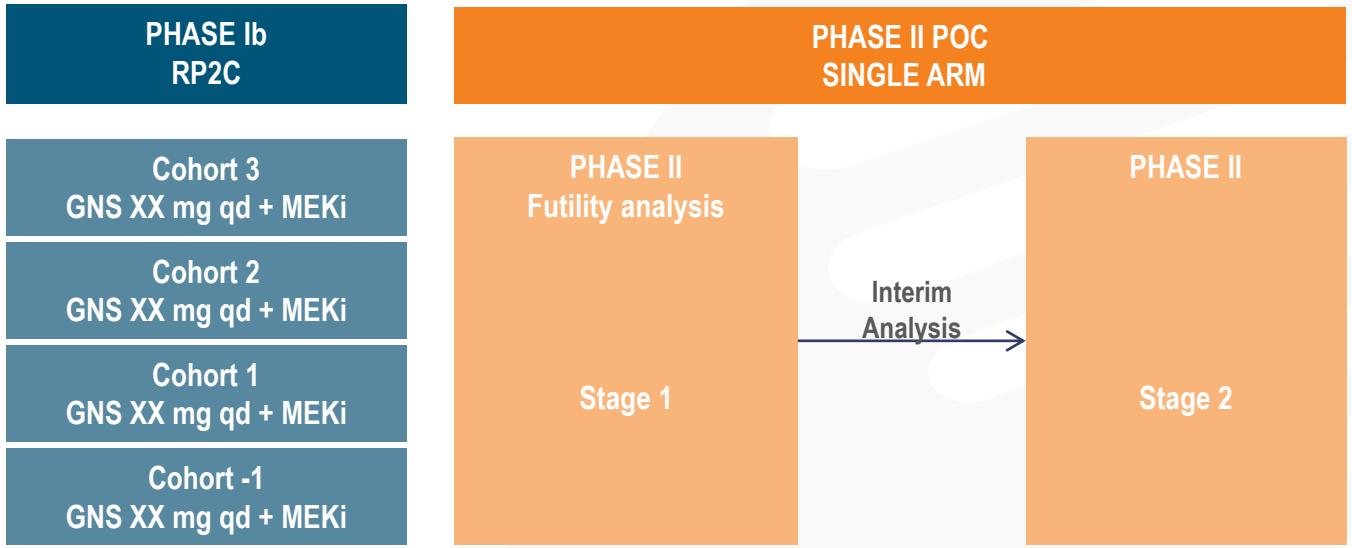
PPT1 expression in liver tissue

-> Safety profile, exposure, and preliminary signal of activity support the investigation of GNS561 in combination

Source: Harding JJ, Awada A, Roth G, Decaens T, Merle P, Kotecki N, Dreyer C, Ansaldi C, Rachid M, Mezouar S, Menut A, Bestion EN, Paradis V, Halfon P, Abou-Alfa GK, Raymond E. First-In-Human Effects of PPT1 Inhibition Using the Oral Treatment with GNS561/Ezurpimtrostat in Patients with Primary and Secondary Liver Cancers. Liver Cancer. 2022 Feb 15;11(3):268-277. doi: 10.1159/000522418.

GNS561 Phase 1b/2a study design

Patients with **KRAS mutated cholangiocarcinoma** who have failed treatment with 1st line treatment and who do not have an actionable mutation (e.g., IDH1, FGFR2)



Endpoints:

Efficacy – objective response rate, progression free survival
Pharmacokinetics
Pharmacodynamics
Safety and tolerability

Cholangiocarcinoma (CCA)

Market opportunity

- *Pascal Caisey, Chief Operating Officer and Chief Commercial Officer of GENFIT*

Estimated market opportunity in Cholangiocarcinoma

Market opportunity

- Epidemiology (*source: IQVIA*)
  - 9,000 new diagnosed patients / y in US
  - 10,000 new diagnosed patients / y in EU5
  - > 66,000 cases/year in the 9MM in 2030
- Market (*source: Olympus Research Global)*
  - Global market of $1.2bn in 2021
  - CAGR expected to reach 12.5% to reach $3.2bn in 2030
- Competitive landscape :
  - Need for new therapy
  - The standard first-line systemic therapy for advanced CCA is a combination of cisplatin + gemcitabine with a median progression-free survival (PFS) 8.0 vs. 5.0 months
  - No approved treatment for KRAS mutation

GNS561 business potential

- Licensing In for GNS561 in US + EU
- GNS561 has been granted Orphan Drug Designation in the US by the FDA
- Several factors could facilitate a shorter time to approval
  - Accelerated approval opportunity given high level of unmet need
  - Single arm study
  - Inclusion of all CCA with KRAS + other mutations
  - Short patient follow up duration

* Source: company projections

Short Q&A (5 minutes)

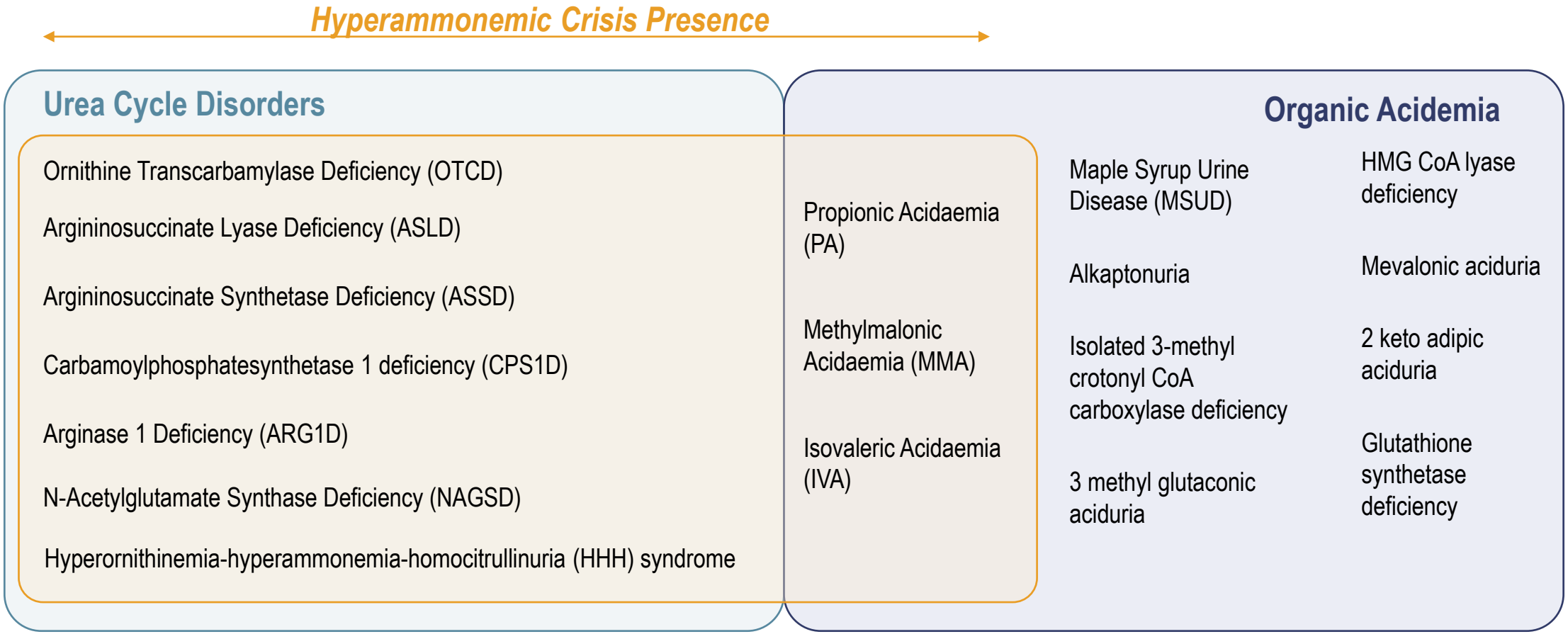
Questions?

Urea cycle disorder (UCD) and organic acidemia disorder (OAD)

Disease state

- *Vincent Forster, PhD, GENFIT, co-founder of VERSANTIS*

Overview of hyperammonenic crises in inborn errors of metabolism

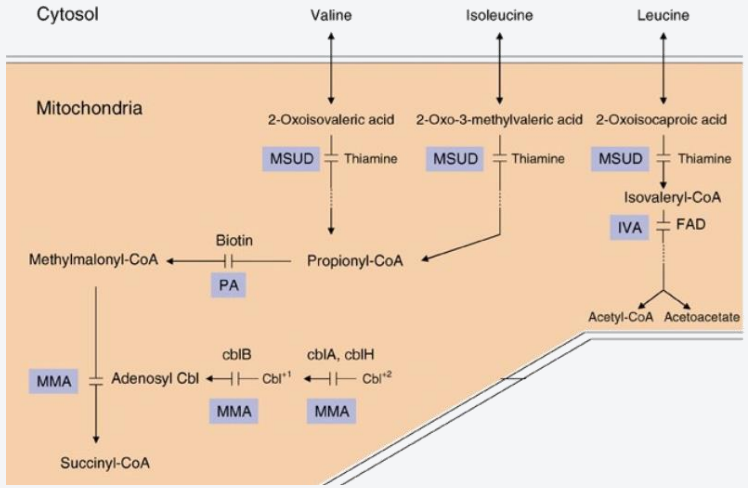


Sources: Maillot et al. (2007), Batshaw et al. (2015), Nettesheim (2017), Martin-Hernandez (2014)

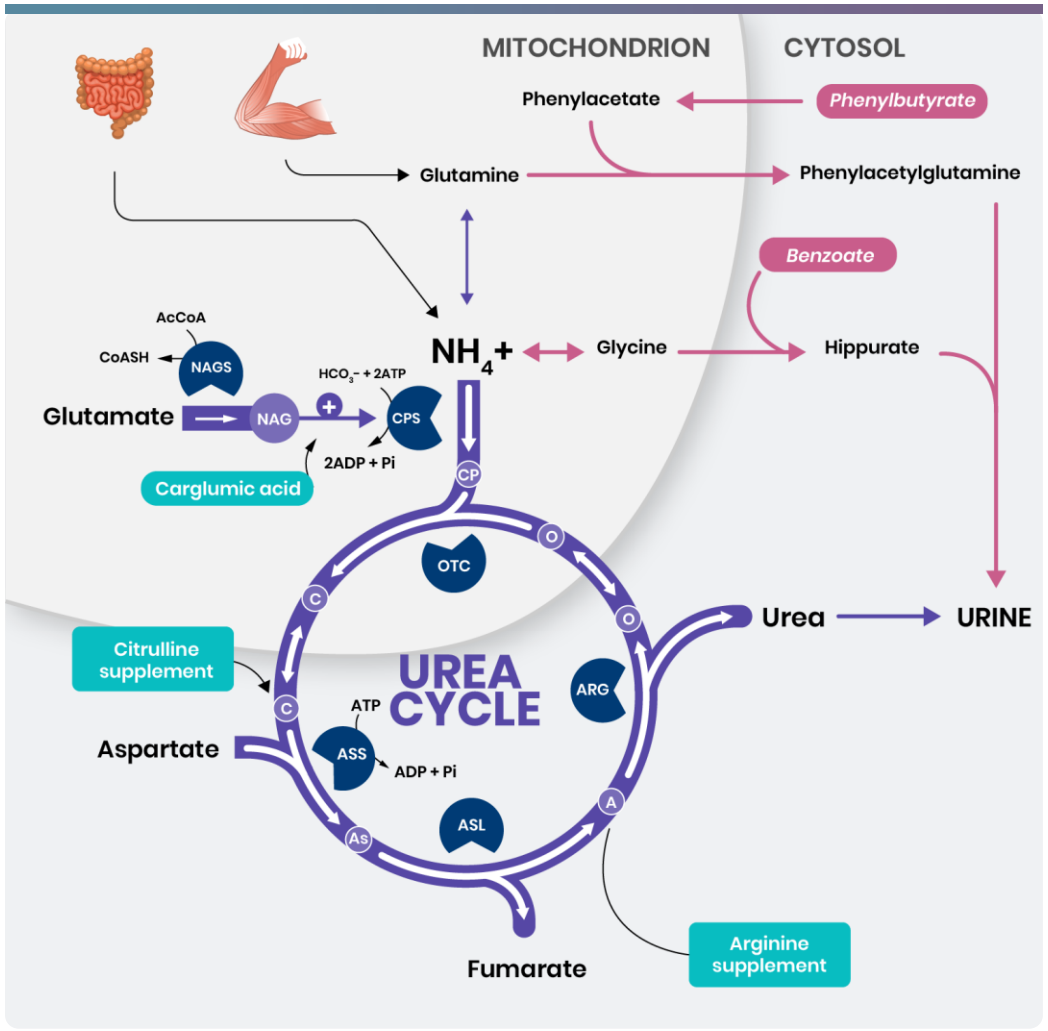
Urgent unmet needs in the treatment of acute hyperammonemic crises (HAC)

- Ultra-rare disease: **1,900 HAC** in children in US + EU5 per year [1,2,3]
- High mortality (75% at 5 years); survivors often have severe brain injuries
- No acute treatment available for early onset crises
- Neonatal hemodialysis is risky, widely unavailable and highly invasive
  - Delays timely critical medical care
  - Ammonia levels rapidly rise

"Classic" Organic Acidemia



Urea Cycle



[1] Summar *et al.*, 2013 | [2] Martin-Hernandez *et al.*, 2014 | [3] Nettesheim *et al.*, 2017

Urea cycle disorder (UCD) and organic acidemia disorder (OAD)

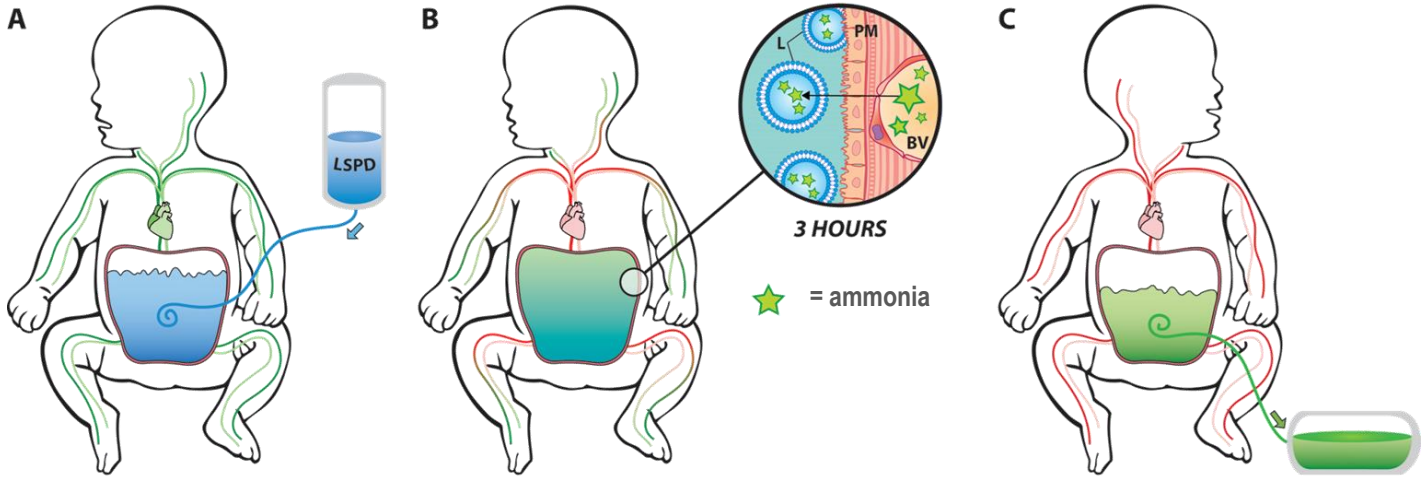
GENFIT's programs: VS-01-UCD*

- *Vincent Forster, PhD, GENFIT, co-founder of VERSANTIS*

* investigational product that is not approved by any health authority

VS-01 is a potential first-line lifesaving treatment for acute hyperammonemic crises (HAC)

- Optimal treatment setup
  - Peritoneal route is well adapted to pediatric patients
  - Rapid treatment onset in all hospitals
  - Complementary to other therapeutical approaches
- Promising data generated via ACLF program
  - VS-01 is optimized for best ammonia removal
  - Consistent efficacy throughout species and from animals to humans
- Regulatory
  - Orphan drug & rare pediatric disease designated (FDA)
  - Projected timelines: IND-ready in 2024
  - Potentially eligible for FDA priority review voucher upon approval



VS-01 ammonia clearance vs. current dialysis modalities

TYPE OF DIALYSIS	BLOOD FLOW (ML/MIN)	DIALYSATE FLOW (ML/MIN)	AMMONIA CL (ML/MIN)	DIALYSIS DURATION (H)	REFERENCES
CPD	NA	NA	1.4 ± 1.1	59 ± 87.2	Arbeiter et al., 2010
CAVHD	16	8.3	2.86	33	Picca et al., 2001
HD	10	500	9.5	9	Picca et al., 2001
HD	15	500	14.4	7.5	Picca et al., 2001
CVVHD	40	33.3	21.5	5.5	Picca et al., 2001
CVVHD	-	-	18.9 ± 7.7	42 ± 30.4	Arbeiter et al., 2010
VS-01 ~ 300 mL (Minipigs 30 mL/kg)	NA	NA	6.0 ± 2.8 – 8.0 ± 3.9	3	Matoori et al., 2020
VS-01 ~ 1 L (Patients 15 mL/kg)	NA	NA	**31.5 ± 16.7**	2	2021 AASLD abstract
VS-01 ~ 2 L (Patients 30 mL/kg)	NA	NA	**74.4 ± 25.0**	2	2021 AASLD abstract
VS-01 ~ 3 L (Patients 45 mL/kg)	NA	NA	**96.8 ± 64.3**	2	2021 AASLD abstract

CAVHD: Continuous Arteriovenous Hemodialysis | HD: Hemodialysis | CVVHD: Continuous Venovenous Hemofiltration | CPD: Continuous Peritoneal Dialysis
Based on CVVHD (Picca *et al.*), ~3 sessions of VS-01 15 mL/kg would be required to decrease ammonemia from 1334 to 139 µg/dL
Sources: Picca *et al.*, Pediatr Nephrol 2001 | Arbeiter *et al.*, Nephrol Dial Transplant 2010 | Matoori S *et al.*, Journal of Controlled Release 2020

KOLs feedback on VS-01 anticipated commercial advantages

- Potential **first-line treatment** for acute hyperammonemic crises
- **Fast implementation** – shorter lead time vs. SOC (extracorporeal hemodialysis)
- **Gentle** as less hemodynamic disturbances and no vascular access damage
- Administered outside the dialysis and intensive care units
- Ease of administration to children, allowing **broader access** to peripheral hospitals

*"If efficacy of VS01 to reduce hyperammonemia is **at least equal to superior to current hemofiltration options, we will switch to VS01** in our neonatology department because of **easier implementation and less hemodynamic** impact on child"– FR Pediatrician*

*"VS01 novel approach is important, very interesting and **fulfils the indication for acute hyperammonemia treatment**. No obstacle to use PD in urgent cases. **PD is a routine technique in ICU for children**" – BE Pediatrician*

*"There's **definitively a space for a VS01** liposomes-based formulation for acute pediatric congenital HA treatment in our center but **also in peripheral centers** (not equipped with HD)" – FR Pediatrician*

*"A key element will be the **speed of action of VS01 to reduce ammonia, compared to hemodiafiltration**. After **30 minutes** of VS01 administration, there're already some significant results. If so, **there's a big potential here!** For child with severe HA, it cannot take days to reduce HA. It's a question of hours to avoid or limit brain damage" – BE Pediatric Head Department*

*"The **closer your clearance is to HD and the lower the complication rate** is with this new liposome-supported therapy, **the more likely I would be to use this therapy rather than HD despite of PD administration**" – USA Children's National Hospital Director*

Source: EU Market Research by external provider, 2015

Note: efficacy outcomes of VS01 vs. SOC subject to clinical trial outcomes

Competitive landscape

Approved drugs	Company	Technology	Population	Limitations
Buphenyl® (US), Ammonaps® (EU), Pheburane® (EU) (Sodium phenylbutyrate)	HORIZON acertherapeutics (US) sobi LUCANE pharma (EU)	Ammonia scavenger	UCDs	- Not approved/effective for acute hyperammonemia
Ammonul® (US) (Sodium phenylacetate and sodium benzoate)	BAUSCH+ Health (US) sobi (EU)	Ammonia scavenger	UCDs	- Associated HE - Insufficient efficacy for acute hyperammonemia (additional hemodiafiltration high flow rate required)
Ravicti® (US, EU) (Glycerol phenylbutyrate)	HORIZON (US) sobi (EU)	Ammonia scavenger	UCDs	- Not approved for acute hyperammonemic events
Carbaglu® (US, EU) (Carglumic acid)	ORPHAN EUROPE RECORDATI GROUP (EU)	Ammonia cycle supplement	UCDs (NAGS deficiency)	- Targets very specific metabolic disorder

Emerging clinical- and preclinical-stage opportunities:

- Ultragenyx (Ph2), aeglea (Ph3), Arcturus therapeutics (Ph2), Boehringer Ingelheim (preclinical),…
- Mostly based on gene therapies and focusing on chronic UCD treatment

Conclusions and forthcoming milestones

VS-01 in HAC

- Demonstrated **superior ammonia clearance** than commercial peritoneal dialysis *in vivo* [1,2,3,4]. Ammonia clearance in adult patients with decompensated cirrhosis at least comparable with hemodialysis [5]
- Received **Rare Pediatric Diseases Designation** and **Orphan Drug Designation** from FDA, for the treatment of urea cycle disorders and hyperammonemia in inborn errors of metabolism. VS-01 could be eligible for a priority review voucher upon its approval by FDA
- Benefits from easier implementation and less hemodynamic impact on child
- Can be swiftly implemented in reference as well as in peripheral centers, hence potentially filling the treatment gap in the emergency treatment of hyperammonemic crises

FORTHCOMING MILESTONES

- Formulation optimization for specific pediatric implementation
- IND-enabling nonclinical studies targeted for completion by 2024

[1] Forster V. *et al. Sci Transl Med* 2014 | [2] Agostoni V. *et al., Adv Funct Mater* 2016 | [3] Giacalone G. *et al., J Cont Release* 2018 | [4] Matoori S. *et al., J Cont Release 2020* | [5] VS-01 Phase 1b data compared to independent published studies

Urea cycle disorder (UCD) and organic acidemia disorder (OAD)

Market opportunity

- *Pascal Caisey, Chief Operating Officer and Chief Commercial Officer of GENFIT*

Estimated* market opportunity for Hyperammonemic Crisis (HAC) in Inborn Errors of Metabolism (IEM)

Market opportunity

- Epidemiology
  - HAC occurs in babies suffering from 2 diseases
    - Urea Cycle Disorder (UCD)
      - 157 babies with UCD / year
      - 2,826 patients with HAC potential up to 18 years old
      - Untreated patients: 45%
    - Organic Acidemia Disorders (OAD)
      - 130 babies with OAD / year
      - 520 patients with HAC potential up to 4 years old
      - No approved drug
- Emergency treatment required during acute crisis
- Global market: $1.5bn in 2021
- Competitive landscape
  - Buphenyl® (US): ~$300k per patient per year / Ammonia scavenger / Patients' population: UCD / Not approved for acute hyperammonemia
  - Ravicti® (US, EU): $950k per patient per year / Ammonia scavenger / Patients' population: UCD / Not approved for acute hyperammonemia

VS01 business potential

- Each year, 1,898 patients could potentially be treated with VS-01 for Hyperammonemia Crisis (HAC)
- VS-01 was granted Rare Pediatric Diseases Designation and Orphan Drug Designation from the FDA for the treatment of urea cycle disorders and hyperammonemia in inborn errors of metabolism
- VS-01 could be eligible for a priority review voucher upon its approval by FDA

Source: all data used in this 2021 assessment come from reference publications (longitudinal and real-world data only, not projections nor modelling)

Short Q&A (5 minutes)

Questions?

Closing remarks

Take home messages

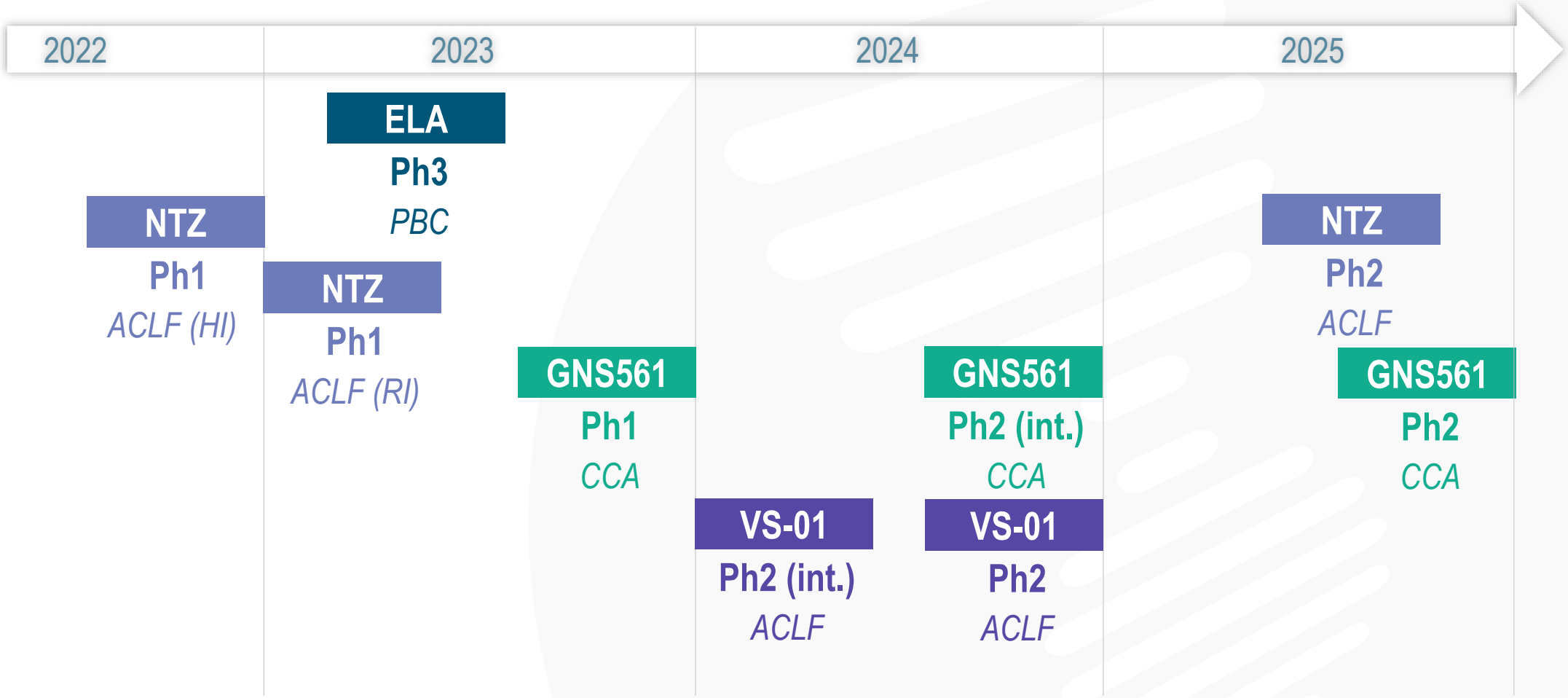
- *Pascal Prigent, CEO of GENFIT*

5 main indications and 6 programs across a variety of development stages (PC/Ph1/2/3)

CHOLESTATIC DISEASES		ACLF		UCD	HE	DIAGNOSIS	
CCA	PBC						
GNS561 *Ph1b/2 start Q4 2022*	ELA *Ph3 data Q2 2023*	NTZ *Ph1 data Ph2 start Q4 2022*	VS-01 *Ph2 start Q4 2022*	VS-01 *Preclinical*	VS-02 *Preclinical*	NASH *Commercia -lization as NASH Next®*	AMMO-NIEMIA TS-01 *Prototype*

- **Expanded pipeline**, including assets with **diversified** mechanisms of action
  - 3 programs in Phase 2 in 2023 (NTZ and VS-01 in ACLF, GNS561 in CCA)
  - 1 Phase 3 readout in 2023 (ELA in PBC)
  - Several research focus in different indications
- Two-fold component: **therapeutics + diagnostic**

A regular newsflow expected for the next 4 years, with several inflexion points (clinical data)



Estimated timelines

Significant opportunities in all therapeutic indications

CHOLESTATIC DISEASES

CCA

$1.2bn
(2021)
$3.2bn
(2030)

(Total market size estimates
Source: Olympus Research Global)

PBC

$330M
(2022)
$1bn
(2025)

(Total 2L market size estimates
Source: Intercept Phamraceuticals
Source: Iqvia Commercial Opportunity Presentation)

ACLF

$4bn
(2030)
$2bn
(2030)

(Total market size estimates. Source: extrapolated from 'Time trend in the healthcare burden and mortality of ACLF in the US' – Hepatology 2016)

UCD (& OAD)

$1.5bn
(2021)

(Total market estimates
Source: company)

HE

$4.1bn
(2026)

(Total market size estimates / Source: Hepatic Encephalopathy Market Report by Coherent Market Insights)

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TOWARDS BETTER MEDICINE

Thank you